Pressure-volume loops in cardiac surgery

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volgens het besluit van het College van Decanen,
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Contents

Chapter 1

Introduction

1.1 Relationships between pressure and volume

Relationships between pressure and volume are part of thermodynamics. They were first employed at the start of the nineteenth century as a result of the industrial revolution, when the interest in steam engines sparked the start of a new theoretical framework now known as thermodynamics. Until then, heat was assumed to be a substance named caloric, but this theory could not explain the principles governing steam engines which were not well understood at that time. The French engineer Carnot took on this challenge and constructed a theoretical model of an ideal heat engine which he applied to study real heat engines (Figure 1-1). Carnot's work ultimately led to the formulation of the Second Law of Thermodynamics which is among the most basic and powerful in physics (or as Einstein put it: *"It is the only physical theory of universal content, which I am convinced [...] will never be overthrown"*[1])

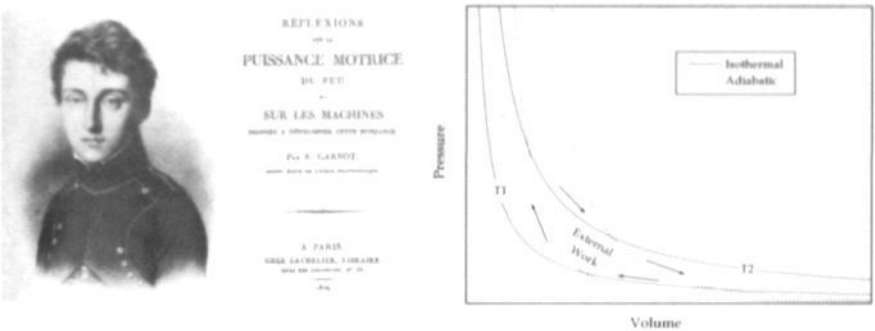

Figure 1-1: Left: Nicolas Sadi Lazare Carnot (1796-1832). French engineer and founder of thermodynamics. Middle: Carnot's pivotal publication "Réflexions sur la puissance motrice du feu...". Right: A Carnot cycle for an ideal gas consisting of reversible phases.

The second law of thermodynamics can be applied to numerous subjects and therefore surfaces in many different forms. The one most useful for this introduction is: *A pressure-volume loop of a maximally efficient engine consists only of reversible phases.* This ideal pressure-volume loop is called a Carnot cycle (Figure 1-1). The Carnot cycle of a heat engine of an ideal gas can be found in every physics textbook; it consists of reversible adiabatic (at constant entropy) and isothermal phases.

Carnot and university thermodynamics deal with heat engines made of an ideal gas. However, this thesis focuses on pressure-volume loops of another thermodynamic subject: the heart. The largest difference with a heat engine is that the heart is a biochemical engine and does not rely on a difference in temperature to perform mechanical work. So, rather than using differences

in temperature as the driving force, a change in biochemical potential should by analyzed.

Although such a "biochemical" thermodynamic analysis is more complicated than the "thermal" case for an ideal gas, the Carnot principle still holds in the human heart[2]: The maximally efficient pressure-volume loop of the heart consists of only reversible phases. In that case the available biochemical energy is maximally converted into mechanical work.

The real pressure-volume loop of the heart, discussed shortly, is not an ideal Carnot cycle. The main deviation is that a certain blood pressure needs to be maintained, so valves and thus isovolumic phases are present in a cardiac pressure-volume loop. However, Carnot's theorem does enable us to define the maximum achievable efficiency with a certain amount of biochemical energy available. It can be shown[2] that Carnot's principles lead to the pressure-volume area concept of Suga[3], which will be introduced in detail later. First the pressure-volume loop of the heart is discussed.

1.1.1 Pressure-volume loop of the heart

During a heart beat, the pressure and volume inside the heart change with time as shown in Figure 1-2. Each beat can be divided into four phases: (isovolumic) contraction, ejection, (isovolumic) relaxation and the filling phase that consists of rapid filling, diastasis and the atrial kick. Note that pressure and volume are out-of-phase; when pressure is high, volume is low and vice versa. A consequence of this phase difference, is that the plot of pressure versus volume results in a loop: the pressure-volume loop.

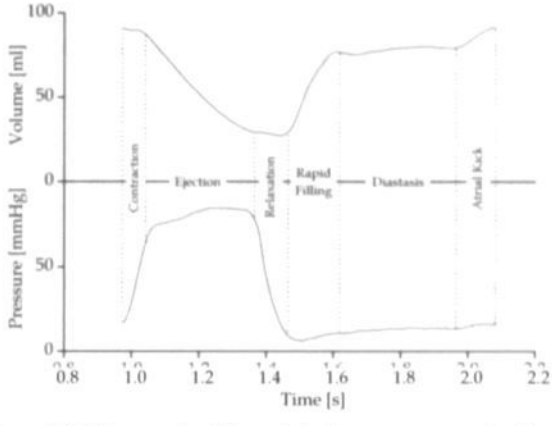

Figure 1-2: Changes in left ventricular pressure and volume over time.

The pressure-volume loop constructed from the data of Figure 1-2 is shown in Figure 1-3. Each heartbeat is represented by one pressure-volume loop. The aforementioned four phases are visible. Starting at the bottom right corner and working counterclockwise, these are: contraction, ejection, relaxation and the filling phase. The four corners of the loop are determined by valve opening and closure. For the left ventricle these are counterclockwise mitral valve closure, aortic valve opening, aortic valve closure and mitral valve opening.

A pressure-volume loop is constructed from the simultaneous measurement of volume and pressure over time, but the variable time is not seen in the loop. Part of the time aspect can be brought back by showing the individual samples as is done on the right in Figure 1-3 (time between points is 12ms). It can be seen that contraction and relaxation are very fast phases, while the filling phase consists of a rapid phase followed by a waiting period, the diastasis. After diastasis, the atrial contribution to filling takes place (atrial kick).

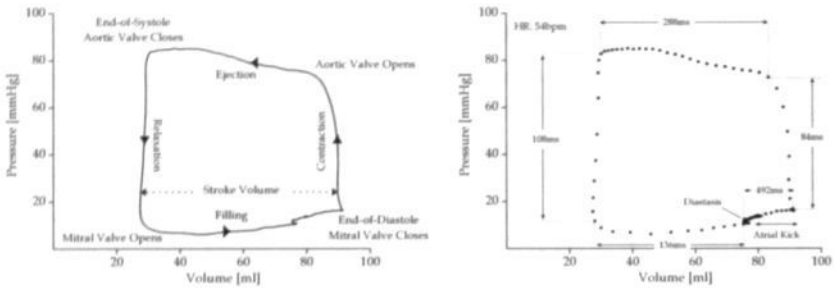

Figure 1-3: A normal left ventricular pressure-volume loop. Left: The four phases and corners of the loops. The width of the loop is the stroke volume. Right: Individual samples of pressure and volume, time between samples is 12ms. The diastasis and the atrial kick can clearly be seen.

The loop of Figure 1-3 is taken from a healthy pig and it has the normal almost rectangular shape. This shape is determined by the valves; in patients with valvular disease the rectangular appearance is lost. In this thesis, two valvular diseases will be discussed: aortic stenosis (Chapter 2) and aortic regurgitation (Chapter 3).

In aortic stenosis, the aortic valve has become too narrow, usually due to calcific deposits on the leaflets. With this disease a high pressure gradient between the left ventricle and the aorta is needed to eject the blood through the stenosis. This results in an ejection phase that is no longer isobaric; the ejection does not occur at constant left ventricular pressure. In the pressure-volume plane, aortic stenosis therefore leads to a "house-shaped" pressure-volume loop (Figure 1-4). In aortic regurgitation, the aortic valve leaks. Due to the leakage, the left ventricle might already be filled during relaxation: the relaxation phase is no longer isovolumic. In a pressure-volume loop this leads to a rounded bottom left corner (Figure 1-4)

In both parts of Figure 1-4 the relation between aortic pressure and ventricular volume is presented. With the help of this novelty, the time point of aortic valve opening and closure can be identified. Furthermore, the high pressure gradient between aorta and ventricle in aortic stenosis is visible. In aortic regurgitation, the fall in aortic pressure during diastole can be seen.

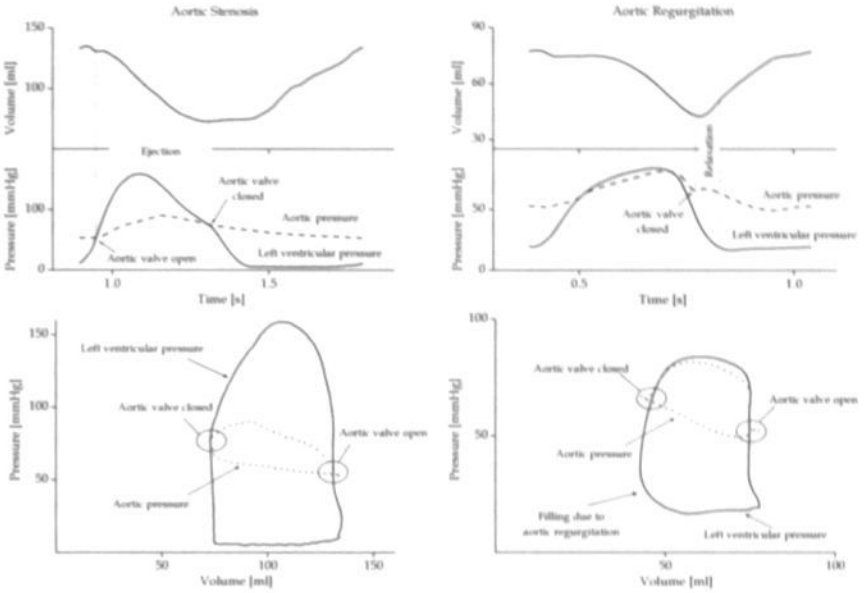

Figure 1-4: Upper left: Left ventricular volume and pressure and aortic pressure over time in a patient with aortic stenosis. Bottom left: Aortic and left ventricular pressure-volume loops in a patient with aortic stenosis. Note the pressure gradient between the left ventricle and the aorta and the triangular "house" shape of the pressure-volume loop.
Upper right: Left ventricular volume and pressure and aortic pressure over time in a patient with aortic regurgitation. Lower right: Aortic and left ventricular pressure-volume loop during aortic regurgitation. The relaxation phase is no longer isovolumic as important filling occurs in this period. The filling pressure is also elevated.

In conclusion, a pressure-volume loop is a graphical representation of the changes in ventricular pressure and volume during a heartbeat. If valvular disease is absent, a pressure-volume loop is rectangular in shape and consists of four clearly delineated phases: contraction, ejection, relaxation and filling.

1.2 Interpretation of pressure-volume loops

In this section the heart and circulation are described from three viewpoints: A thermodynamic, physiological and an empirical viewpoint. In all three, data obtained by pressure-volume loops play a crucial role.

1.2.1 The heart from a thermodynamic viewpoint

From a thermodynamic viewpoint the heart is a converter of biochemical energy into mechanical energy. It is a consequence of the second law of thermodynamics that this conversion can not occur without heat production, meaning a loss of useful energy. This heat production can be measured and the sum of the heat produced and the work done by the heart is equal to the total chemical energy consumed, as predicted by the first law of thermodynamics[4]. Assuming fully aerobic metabolism, the available chemical energy can be calculated by multiplying the oxygen consumption of the heart by its energy equivalent, which is the total energy released when oxidizing carbohydrates, fat or protein (about 20 J per mole O_2)[4].

A commonly used energy transfer diagram[3] is shown in Figure 1-5 outlining the steps from oxidation to the work performed by the ventricle as well as their efficiency. The overall efficiency of the heart (external work divided by oxygen consumption) is about 25% in a normal heart[5]. The remainder is the heat loss.

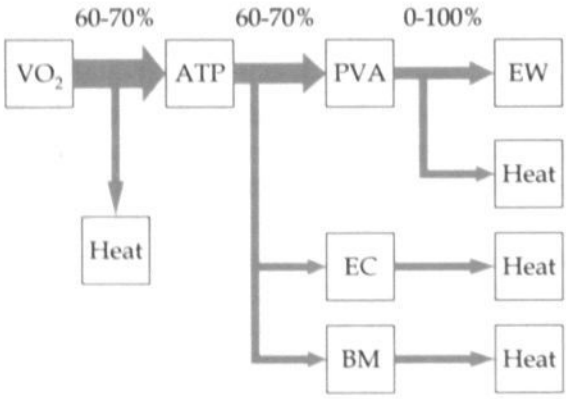

Figure 1-5: Efficiency of the conversion of chemical energy to external work. VO_2: Energy released during oxidation of carbohydrates, fat and protein; ATP: Adenosine triphosphate; EC: Excitation-contraction coupling; BM: Basal metabolism; PVA: Pressure-volume area; EW: External work. Modified from Suga[3].

The variables myocardial oxygen consumption VO_2, pressure-volume area PVA and external work EW can relatively easily be measured and the VO_2-PVA-EW relation is therefore intensively studied (see Figure 1-6). The classic work in this field by Suga[3] has the key result that the pressure-volume area is proportional to the oxygen consumption[6], as shown in Figure 1-6. The PVA to EW conversion efficiency depends on loading conditions[7] and is essentially the result of the Starling mechanism to be discussed later.

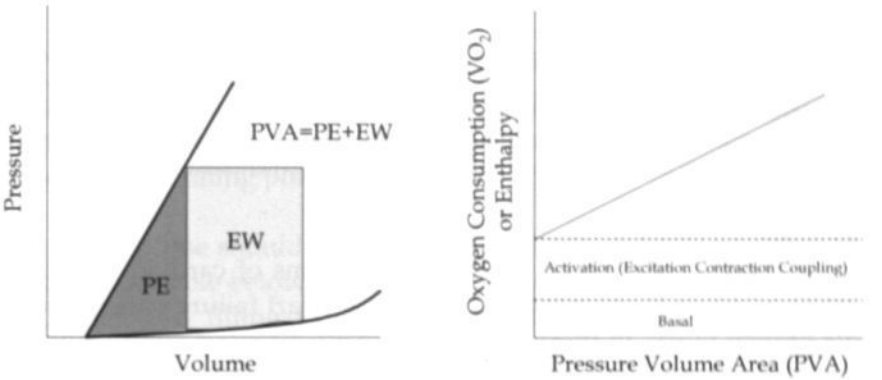

Figure 1-6: Left: Definition of pressure-volume area (PVA) as the sum of external work (EW) and potential energy (PE) (which is energy released if the contraction would continue and the ventricle could fully eject). Right: Oxygen consumption is linearly related to pressure volume area. Redrawn from Westerhof[5].

An example of the usefulness of the PVA-concept is the demonstration that pressure work is less efficient than volume work[8]. This is illustrated in this thesis in Chapter 6 which describes an experiment done during acute mitral regurgitation. It was observed that coronary blood flow was not increased when acute mitral regurgitation was created while external work strongly increased. Figure 1-7 shows the pressure-volume loops before and during mitral regurgitation. Stroke volume increases threefold, while pressure volume area and thus oxygen consumption are barely changed.

The thermodynamic approach, more commonly referred to as ventricular energetics, is used to study the ventricle with questions such as:

- Can the ventricle improve its efficiency (e.g. ischemic preconditioning[9])?
- Which part of the energy transfer changes with disease (e.g. myocardial stunning[10] or heart failure[11,12])?
- Is the heart designed to maximize external work or to maximize its efficiency and what happens in the diseased heart[7]?

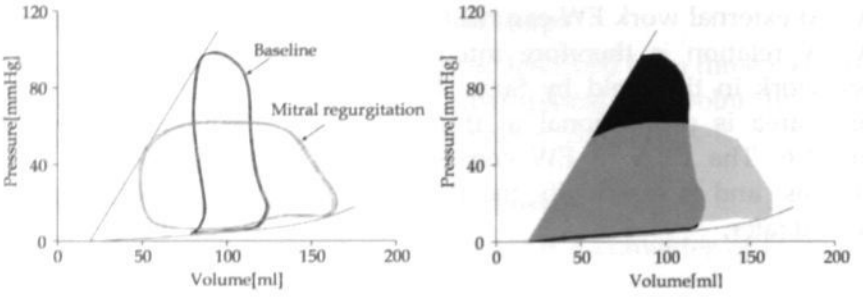

Figure 1-7: Pressure-volume loops (left) and area (right) before and during acute mitral regurgitation. The stroke volume increases strongly during acute mitral regurgitation with the higher preload. In contrast, pressure-volume area barely changes so oxygen consumption is the same before and during acute mitral regurgitation. For this reason no change in coronary blood flow was observed during the experiments.

Others investigate the effects of therapy in terms of cardiac efficiency[13-15]. The latest addition is biventricular pacing for heart failure patients with left bundle branch block. In these patients, an asynchronous contraction occurs because not all parts of the left ventricle are simultaneously activated. Resynchronization by pacing restores the synchronous contraction and increases cardiac efficiency[16].

In conclusion, in energetic studies pressure-volume loops are applied to determine pressure-volume area and external work. Furthermore, by measuring the pressure-volume area and oxygen consumption at different loading conditions and contractility, their relation can be determined.

1.2.2 The heart from a physiological viewpoint

In physiology one often describes the cardiac pump by stating the Starling law of the heart. This law reads that "the greater the heart is *filled*, the greater will be the quantity of blood *ejected* into the aorta"[17]. So both the filling characteristics (diastolic function) and the ejection properties of the heart (systolic function) are important. The assessment of diastolic and systolic function with the help of pressure-volume loops is the subject of this paragraph.

Diastolic function

The goal of diastole is to fill the heart. Although the exact start and duration of diastole is disputable[18], in this thesis diastole is defined as compromising the relaxation and filling phase.

The relaxation phase should be as short as possible and pressure should fall as quickly as possible below atrial pressure, to allow the mitral or tricuspid valve to open and filling to start. The parameters describing the fall in pressure and the duration of the relaxation phase are given in Table 1-1. This table includes a summary of typical values found in literature.

Table 1-1: Normal and abnormal values for left ventricular relaxation phase parameters.

Variable	Unit	Normal	Abnormal	Reference*
$dPdt_{min}$	mmHg s^{-1}	2660	<1260	19
	mmHg s^{-1}	2922	<1422	19
	mmHg s^{-1}	1864	<1084	19
	mmHg s^{-1}	1825	<1303	19
	mmHg s^{-1}		<1100	20
	mmHg s^{-1}	1830	<1232	21
τ	ms	38	>52	19
	ms	33	>49	19
	ms	31	>37	19
	ms		>48	20
	ms	46	>70	21
	ms	43	>67	22
IVRT	ms		>100	23
PHT	ms	27	>39	22

$dPdt_{min}$: Maximum negative left ventricular pressure derivative; τ: Time constant of left ventricular pressure decay (exponential fit); IVRT: Isovolumic relaxation time; PHT: Pressure half-time, time from $dPdt_{min}$ to 50% of the left ventricular pressure at $dPdt_{min}$.
*If the reference does not give a normal and abnormal value, abnormal value are based on two times standard deviation.

The relaxation phase can be prolonged due to heart disease. A typical example is hypertrophy due to aortic stenosis which is the subject of Chapter 2. The problem with a prolonged relaxation phase is that filling can only start if ventricular pressure is lower than atrial pressure. So, the longer

the relaxation phase, the less time there is available for filling. The main compensatory mechanism of a prolonged relaxation phase, is an increase of filling pressure.

The filling phase starts when the mitral valve opens (although with valvular regurgitation filling can also occur during the relaxation phase, see Figure 1-4). Normal filling starts with a rapid filling phase in which the heart actively sucks blood from the atrium[18]. Then a rather long pause occurs, called diastasis. Next, the atrium actively fills the heart by contracting and emptying its content into the ventricle. Immediately after the atrial contraction, the contraction of the ventricle starts. The parameters describing the filling phase are given in Table 1-2.

Table 1-2: Normal and abnormal values for left ventricular filling phase parameters

Variable	Unit	Normal	Abnormal	Reference*
EDVI	ml m^{-2}	72	>102	24
	ml m^{-2}	70	>110	24
	ml m^{-2}	79	>101	24
	ml m^{-2}	71	>111	24
	ml m^{-2}	77	>107	25
	ml m^{-2}	93	>105	26
	ml m^{-2}	82	>112	22
LVP_{ED}	mmHg		>16	20
	mmHg	11	>19	21
	mmHg	8	>12	27
	mmHg	12	>22	28
PFR_{early}	EDV s^{-1}	3.3	<2.1	19
	EDV s^{-1}		<1.6	20
	EDV s^{-1}	3.2	<2.6	29
	ml s^{-1}	483	<261	21
	ml s^{-1}	330	<188	29
	ml s^{-1} m^{-2}		<160	20
	ml s^{-1} m^{-2}	269	<87	22
tPFR	ms	136	>182	19
	ms	140	>160	29
E/A			<0.5	20
		1.9	<0.9	30
		1.4	<0.8	30
C_{dia}/E_{cd}	ml $mmHg^{-1}$	6.12	<3.7	31
	ml $mmHg^{-1}$	10.0	<7.0	31
	ml $mmHg^{-1}$	17	<10	32
	ml $mmHg^{-1}$	13.3		33
K_c/β	ml^{-1} m^{-2}	0.032	>0.060	21
	ml^{-1} m^{-2}	0.044	>0.096	22

EDVI: Left ventricular end-diastolic volume index; LVP_{ED}: Left ventricular end-diastolic pressure; PFR_{early} : Peak filling rate during the first part of diastole; tPFR: Time to peak filling rate; E/A: Ratio between early and late peak filling rate; C_{dia}/E_{cd}: Slope of the relation between end-diastolic pressure and volume, linear fit K_c/β: Slope of the relation between end-diastolic pressure and volume, exponential fit.
*If the reference does not give a normal and abnormal value, abnormal value are based on two times standard deviation.

The end result of the filling phase is the end-diastolic volume or **preload** of the ventricle. The preload depends on the filling pressure and the compliance of the ventricle in diastole. By varying the filling pressure (e.g. by caval vein occlusion), the end-diastolic pressure-volume relation can be drawn. This relation is curvi-linear and gives an impression of chamber stiffness (Figure 1-8). A steep end-diastolic pressure-volume relation indicates a stiff ventricle, as more pressure is needed to fill the ventricle.

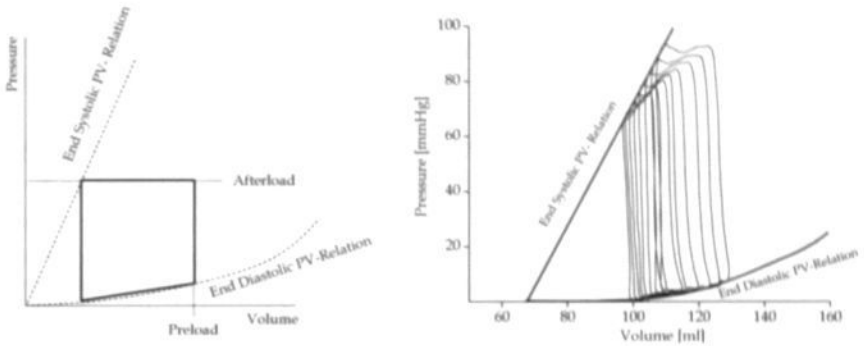

Figure 1-8: Left: Preload, afterload, end-diastolic and end-systolic pressure-volume relation. Right: Inferior caval vein occlusion reduces preload and afterload of the left ventricle. The end-systolic and end-diastolic pressure-volume relation can then be drawn.

The filling phase may be abnormal in heart disease. As discussed above, the relaxation phase can be so long that rapid filling is not possible. Furthermore, the ventricle may be too stiff, which can be the case in aortic stenosis patients (Chapter 2). In these patients the heart muscle thickens (hypertrophy) in order to maintain enough strength to eject through the narrowed valve.

Pathologic hypertrophy causes a severely prolonged relaxation phase and a stiffer muscle which eventually leads to diastolic heart failure. Here filling pressure becomes so high that congestion occurs in the lungs, causing pulmonary edema, or a filling that is inadequate for the required output. In Figure 1-9 the end-diastolic pressure-volume relation is drawn for six aortic stenosis patients. Clear differences can be observed: Some patients have a very stiff ventricle, while others have a normal, flat end-diastolic pressure-volume relation. This difference may be prognostically significant.

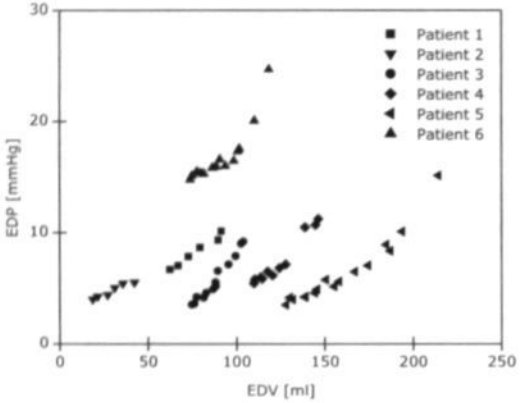

Figure 1-9: End-diastolic pressure volume relation in six aortic stenosis patients. Patient 6 has a very stiff ventricle and requires extreme filling pressures.

Systolic function

Systole starts at the end-of-diastole and compromises the contraction and ejection phases. The goal of systole is to eject blood into the aorta.

In the contraction phase, the pressure in the ventricle rapidly rises to achieve a pressure high enough to open the aortic or pulmonary valve. Contraction is usually the fastest phase (see Figure 1-3). Parameters describing the left ventricular contraction phase are given in Table 1-3. The parameter most often used is the maximum of the ventricular pressure derivative, $dPdt_{max}$, as this parameter is directly linked to the strength of the cardiac contraction and thus to the heart muscle's condition. As $dPdt_{max}$ is highly preload dependent, the slope of the $dPdt_{max}$ versus preload (end-diastolic volume) relation is sometimes applied[34].

Table 1-3: Normal and abnormal values for left ventricular contraction phase parameters

Variable	Unit	Normal	Abnormal	Reference*
$dPdt_{max}$	mmHg s^{-1}	1610	<1030	19
	mmHg s^{-1}	1670	<1030	19
	mmHg s^{-1}	1661	<1015	19
	mmHg s^{-1}	1677	<811	21
dPdtMax vs. EDV	mmHg s^{-1} ml^{-1}	23		35
$(dP/dt/P)_{max}$	s^{-1}	44	<27	19
$[(dP/dt)/DP]_{DP=40}$	s^{-1}	38	<13	19

$dPdt_{max}$: Maximal left ventricular pressure derivative; dPdtMax vs. EDV: Slope of the relation between $dPdt_{max}$ and end-diastolic volume during preload reduction; $(dPdt/P)_{max}$: Maximal ratio of left ventricular pressure derivative and left ventricular pressure; $[(dP/dt)/DP]_{DP=40}$: Ratio of left ventricular pressure derivative and developed left ventricular pressure at 40mmHg of developed pressure.
*If the reference does not give a normal and abnormal value, abnormal value are based on two times standard deviation.

The ejection phase starts at the opening of the aortic or pulmonary valve and ends at the end-systolic point. During ejection the sarcomeres of the ventricle need to shorten but first they have to develop enough force to overcome the systolic ventricular pressure. Systolic ventricular pressure[36] is therefore called **afterload** but, because it is easier to measure, one often assumes systolic blood pressure to be a measure of left ventricular afterload*.
The goal of many therapies (beta-blockade, nitroprusside, IABP), is a reduction in afterload as this leads to either an increase in stroke volume (see Figure 1-10) or a reduction in myocardial oxygen consumption (see previous paragraph).

The end-systolic point marks the end of ejection. The volume and pressure at end-of-systole are determined by the afterload and the end-systolic pressure-volume relation (Figure 1-8). Like the end-diastolic relation, the end-systolic pressure volume relation can be determined during caval vein occlusion[37]. The position and especially the slope of this relation, Ees, is an indicator for the intrinsic strength of the ventricle, the **contractility**. The higher the contractility, the steeper the slope of the end-systolic pressure-volume relation. In Table 1-4 a number of ejection phase indices are given.

Starling's law: Preload, Afterload & Contractility

From the previous paragraph, the quantities preload, afterload and contractility emerge as the key variables to describe the cardiac function. These will be summarized with the aid of the pressure-volume loops of Figure 1-10.

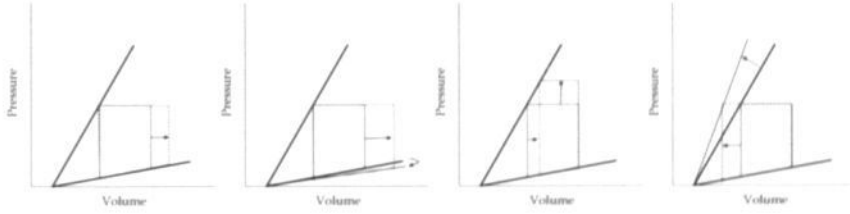

Figure 1-10: From left to right: Effect on pressure-volume loop of an increase in filling pressure (increased preload), positive lusitropy (increased preload), afterload and positive inotropy (increased contractility)[8].

* The correct definitions of preload and afterload are the wall stress at end-of-diastole and the wall stress during ejection, respectively. Wall stress is related to volume, pressure and wall thickness of the ventricle via Laplace's law. In this thesis a common simplication is made: End-diastolic volume is taken as preload and systolic left ventricular pressure is taken as afterload.

Preload is the end-diastolic volume which can be increased by increasing the filling pressure or decreasing the stiffness of the ventricle. An increased preload leads to more ejection (Starling's law).
Afterload is systolic ventricular pressure. An increase in afterload leads to a decrease in ejected blood.
Contractility is the intrinsic strength of the muscle; it is represented in the pressure-volume plane by the end-systolic pressure-volume relation. An increase in contractility leads to an increased stroke volume.

Table 1-4: Normal and abnormal values for left ventricular ejection parameters

Variable	Unit	Normal	Abnormal	Reference*
ESVI	ml m^{-2}	20	>36	24
	ml m^{-2}	24	>44	24
	ml m^{-2}	28	>40	24
	ml m^{-2}	30	>50	24
	ml m^{-2}	29	>45	25
	ml m^{-2}	37	>43	26
	ml m^{-2}	28	>42	22
SVI	ml m^{-2}	45	>71	23
	ml m^{-2}	58	>68	26
LVP_{max}	mmHg	130	<90, >140	27
	mmHg	119	<77, >161	25
	mmHg	121	<101, >131	26
	[illegible]	[illegible]	[illegible]	[illegible]
SW(I)	g m	81	<35	19
	g m m^{-2}	53	<9	19
	g m m^{-2}	41	<17	19
	joule m^{-2}	0.76	<0.62	26
EF	%	72	<56	19
	%		<45	20
	%	62	<48	25
	%	66		22
MNSER	EDV s^{-1}	3.3	<1.6	19
Ees	mmHg ml^{-1}	2.7	<2	31
	mmHg ml^{-1}	2.0	<1.4	31
	mmHg ml^{-1}	2.0		25
	mmHg ml^{-1}	2.5		33
	mmHg ml^{-1}	2.0		32
	mmHg ml^{-1}	3.0		35
	mmHg ml^{-1}	1.8		28
PRSW	mmHg	101	<76	31
	mmHg	90	<74	31
	mmHg	53	<21	35
	mmHg	62	<30	38

ESVI: End systolic volume index; SVI: Stroke volume index; LVP_{max}: Maximal left ventricular pressure; SW(I): Stroke work index; EF: Ejection fraction; MNSER: mean normalized systolic ejection rate; Ees: Slope of the relation between end systolic pressure and volume during preload reduction; PRSW: Preload recruitable stroke work, slope of the relation between stroke work and end-diastolic volume during preload reduction.
*If the reference does not give a normal and abnormal value, abnormal value are based on two times standard deviation.

The right ventricle

The focus in this paragraph was the left ventricle, as this thesis primarily deals with the left ventricle. However, most of this section equally applies to the right ventricle, but this ventricle is much less studied as it is the left ventricle that is often the problem in heart disease. Normal and abnormal values for parameters describing right ventricular function are therefore difficult to find in the literature. Some of them are given in Table 1-5.

Table 1-5: Normal and abnormal values for right ventricular function.

Variable	Unit	Normal	Abnormal	Reference*
RVEDV	ml	176		39
RVESV	ml	149		39
RVP_{max}	mmHg	25	<15, >30	27
	mmHg	35		39
RVP_{ed}	mmHg	4	>7	27
	mmHg	4		39
RVSW	mmHg ml	500		39

RVEDV: Right ventricular end-diastolic volume; RVESV: Right ventricular end-systolic volume; RVP_{max}: Maximal right ventricular pressure; RVP_{ED}: Right ventricular end-diastolic pressure; RVSW: Right ventricular stroke work.
*If the reference does not give a normal and abnormal value, abnormal value are based on two times standard deviation.

1.2.3 The heart from an empirical viewpoint

Physics and medicine are both empirical sciences, but when trying to perform physical measurements in the body, one is inevitably confronted with the many interactions between the system of interest and the rest of the body. Likewise, the in-situ heart is not an isolated pump. It is part of the circulation and is servo-controlled by many feedback mechanisms. In a classic article by Guyton[40], the circulation and its regulation are described as a block scheme, depicted in Figure 1-11. Because of this intense regulation and the many negative feedback mechanisms, the system is extremely stable. However, from an empirical standpoint, this stability has some negative aspects: it is difficult to see from the end-result (flow and pressure) whether a certain part is dysfunctional. Likewise it is difficult to know the cause of certain changes in pressure and flow.

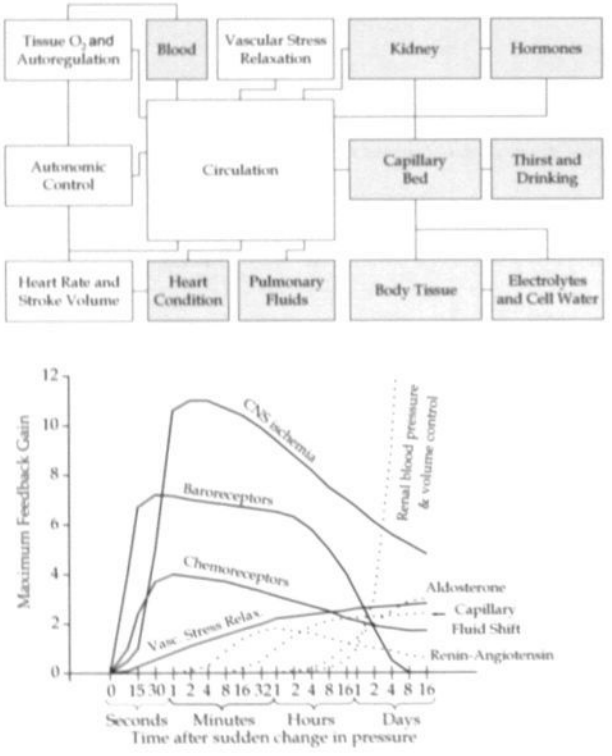

Figure 1-11: The overall regulation of the circulation[17,40]. Top: The circulation and its regulatory mechanisms. The central circulation block compromises the heart and all vessels. All other blocks have a direct or indirect interaction with the circulation. The grey shaded blocks are slow mechanisms taking more than 5 minutes to react to sudden changes in blood pressure. Bottom: The feedback gain and response time of various regulatory mechanisms.

In cardiac surgery, the heart is the organ of interest and it is thus cardiac information that needs to be extracted from the complex circulation system. The first and obvious step, is to identify the key cardiac function variables. Secondly, to separate cardiac information from other systems, the circulation is disturbed via an intervention. The third step used in this thesis, is to eliminate possible variables by measuring quickly after an intervention. All three steps are now discussed in detail.

Key cardiac function variables: Preload, Afterload, Contractility & Heart Rate

As described in the previous section on heart physiology (1.2.2), the stroke volume of the ventricle is determined by how well it is filled (preload), the pressure against which it has to eject (afterload) and the intrinsic strength of the ventricle (contractility). These three parameters and a fourth one, the heart rate, determine cardiac output (liters per minute). To a large extent, preload, afterload and heart rate are determined by the regulatory mechanisms of Figure 1-11 and not by the heart itself. In contrast, contractility is much more a heart muscle property which is only mildly regulated.

The fundamental question when assessing a change in heart function are thus: Is there a change in preload, afterload, contractility, heart rate or a combination? Heart rate, left ventricular afterload and right ventricular preload can be estimated with relative ease (by distal arterial and venous pressure measurement). The determination of left ventricular preload and right ventricular afterload is more difficult and often requires a direct pressure measurement at the point of interest by catheterization. A good contractility measurement is even more difficult; one of the best contractility indices is probably the slope Ees of the end-systolic pressure-volume relation[19], as described in the previous paragraph.

The strength of pressure-volume loop measurements (with the help of a conductance catheter) is the ability to determine all key cardiac function variables.

Disturbing the system via interventions

One way to characterize a highly regulated system such as the circulation, is by disturbing it. In this thesis the interventions applied are: Cardiac tilting, caval vein occlusion, acute mitral regurgitation and switching mechanical support on and off. One of the goals of these interventions, is to establish a chain of events. An example of this approach is presented in Figure 1-12.

This approach can only be used if the method of measurement is continuous and has a sufficiently high sample frequency. Pressure-volume loop measurements with a conductance catheter have these properties.

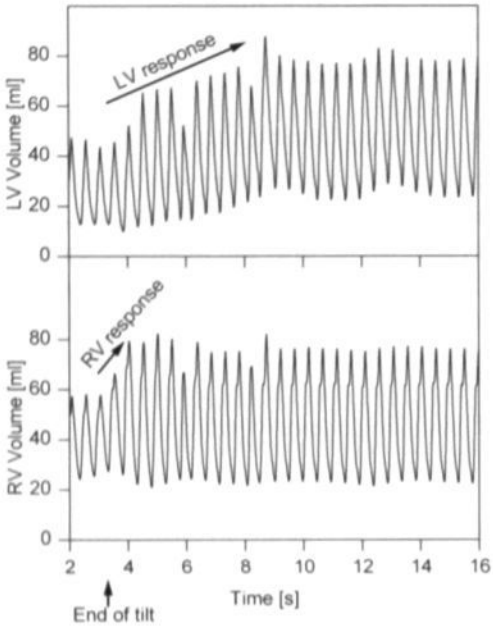

Figure 1-12: Changes in left and right ventricular volume upon repositioning of the heart from a tilt into its normal position. The right ventricle immediately responds to the new situation by an increase in end-diastolic volume within two to three beats. In contrast, the left ventricle slowly accommodates to the new situation in about ten beats.

Limiting the variables: the time factor

The response of the heart to changes in preload, afterload and heart rate are instantaneous, while changes in contractility are either very quick (e.g. ischemia[41]) or take quite a long time (as in hypertrophy).

One way to remove some of the complexity of the circulation is therefore by time. If measurements can be done quickly, the heart response can be detected while many of the feedback mechanisms mentioned in Figure 1-11, have not yet kicked in. In this thesis this approach is used many times. Usually measurements are done within 5 minutes after an intervention so that all the grey blocks from Figure 1-11, can be excluded from the analysis. Even more so, preload variation by caval vein occlusion takes only seconds, and not one of the feedback mechanisms is quick enough to respond. This leads to an evaluation of only the heart itself, which, as mentioned before, can be used to measure contractility and stiffness of the ventricle.

Again, this approach requires a method of measurement that can detect changes quickly, preferably beat-to-beat.

In conclusion, pressure-volume loops, if measured by a conductance catheter, give a beat-to-beat, continuous, and high sample-frequency measurement of all the key cardiac function variables. From an empirical standpoint it is therefore the ideal measuring tool to investigate the heart itself and the loading conditions under which it has to operate.

1.3 Measurement of pressure-volume loops

1.3.1 Available techniques

The determination of a pressure-volume loop requires simultaneous measurement of ventricular pressure and volume over time. Since pressure can only be measured in the cavity where it exists, a non-invasive measurement of pressure-volume loops is not possible. So, true left ventricular pressure-volume loops require invasive testing, although systolic parameters may be determined by combining arterial pressure measurement at proper time delay with non-invasive volume measurements, e.g. by echocardiography[42,43].

Pressure

The most common invasive pressure measurement method is the one in which an extracorporeal pressure sensor is connected to a fluid-filled catheter with its end hole placed at the site of interest (i.e. the ventricle). The main drawback of this method is its limited frequency response: the column of water serves as a low-pass filter with a typical cut-off frequency of around 20Hz[44]. This is especially troublesome when measuring ventricular pressure, as the rapid up and down stroke of pressure causes high frequencies to be present in the signal. Another drawback is that the position of the sensor relative to the catheter's end-hole is crucial to ensure that no inappropriate hydrostatic pressure is included. Finally, fluid-filled systems are susceptible to motion artifacts such as the whipping of the catheter during a heartbeat.

Miniature pressure transducers mounted on the tip of a catheter are more expensive but do not have the drawbacks of fluid-filled systems[44]. Currently two miniature pressure transducers are widely used, the brands Millar (Millar Instruments, Houston, TX)[45] and Sentron (Sentron/CD Leycom, Zoetermeer, The Netherlands). Both are based on the piezoresistive effect: the resistance of a material changes when a mechanical force is applied. More recently a fiber-optic method of blood pressure measurement has been proposed, but this technique has not yet been extensively validated in humans[46].

Volume

The in-vivo volume measurement can be carried out in a number of ways. Most are derived from images acquired by a variety of techniques followed by dimensional measurements.

The most common technique to determine ventricular volume, is echocardiography which in combination with edge contour analysis can give online ventricular area[43]. This method has been found to be reasonably accurate at least for steady state conditions[47-49]. Worse results have been obtained at interventions such as preload reduction by caval vein occlusion[47,48]. Another drawback of echocardiography is its limited sample frequency of about 30Hz[42,43].

With ventriculography the area of the ventricle is measured under fluoroscopy during a contrast injection. It requires a ventricular edge detection algorithm, much like echocardiography. The main drawbacks of ventriculography are that it requires a fluoroscopy system, that the sample frequency is limited to about 30Hz and that the volume is only available after significant post-processing and cannot be obtained continuously[50].

Radionuclide angiocardiography is very similar to ventriculography, but it instead of a contrast material and fluoroscopy, a radioactive material is used in combination with a gamma camera. The main disadvantages of this method are it being rather cumbersome, its use of radioactive materials, the limited sample frequency of approximately 20Hz and the post-processing required to obtain the volume data[51].

Another, less often applied technique is anatomical mapping, which gives an accurate 3D picture of the ventricular cavity[52], but requires tremendous acquisition times, limiting its use for pressure-volume loops. Newer techniques, not extensively validated in humans, are magnetic resonance imaging and the transcardiac conductance technique[53,54].

This thesis focuses on an alternative method for measuring pressure-volume loops, the conductance catheter technique. It has the advantage that it measures volume at a high frequency (250Hz or higher), in real time and continuously making it ideal to measure pressure-volume loops.

1.3.2 Conductance catheter technique

The conductance catheter was developed by Baan and colleagues in Leiden[55] and measures volume via the conductance of the blood in the ventricular cavity. The conductance method is based on the realization that the conductance G of a cylinder with cross-sectional area A, length L made of a homogeneous, pure-resistive material with resistivity ρ is related to its volume V by the following equation:

$$(1) \qquad G = \frac{A}{\rho L} = \frac{V}{\rho L^2}$$

This concept is applied in the heart by positioning a catheter carrying a sequence of electrodes in the right or left ventricle. A known current is applied inside the ventricle via the four outer electrodes. Then the voltage difference is determined across each inner electrode pair, and the conductance of a particular segment can be calculated. By summing up the individual segments, the total conductance and thus volume can be determined. This is illustrated in Figure 1-13.

To convert the segmental conductance (in Siemens) to the volume (in ml) of the ventricle the following equation is applied:

$$(2) \qquad V = \frac{\rho}{\alpha} L^2 \sum_{1}^{N} G_n - V_{pc}$$

In this equation L is the inter-electrode distance and G_n is the measured conductance of segment n. In order to obtain the absolute volume V, three parameters need to be known: resistivity ρ, parallel conductance V_{pc} and slope factor α. These parameters vary between patients, with the position of the catheter in the ventricle and with blood properties. Therefore they need to be determined each time via calibration measurements.

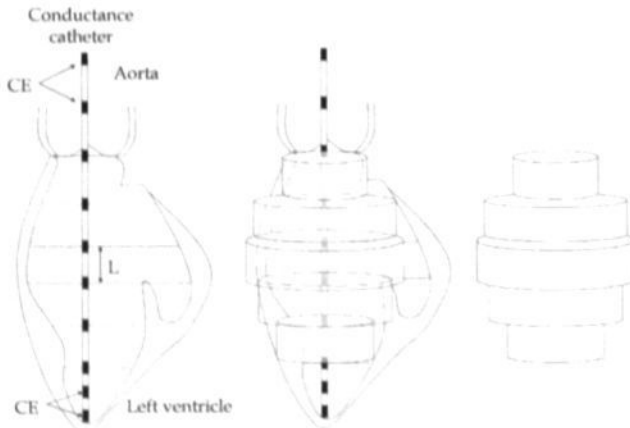

Figure 1-13: The conductance catheter measures the volume of the ventricle by summing up the conductance of individual segments. The ventricle is thus modeled as a stack of cylinders. CE=Current electrode; L=interlectrode distance.

Conductance catheter calibration

The calibration procedure to obtain ρ, V_{pc} and α used in all studies is:
First, the resistivity ρ of the blood of the patient is measured. This is done be measuring the conductance of a cylinder of blood with known dimensions. Via equation (1) the resistivity can then be determined.

Second, the parallel conductance V_{pc} is determined. It corrects for the fact that the tissues surrounding the blood in the ventricle are also conductive materials (i.e. the heart muscle and the other ventricle but not the lungs[56]). The parallel conductance is measured via hypertonic saline injection[57].
Third, the slope factor α needs to be determined. Commonly one argues that this factor corrects for any volume the catheter 'misses' at the top and bottom of the ventricle (see Figure 1-13). But more correctly, the slope factor also corrects for the fall of the electric current density at the edges of the ventricle[58,59]. It is measured by comparing conductance derived stroke volume to actual stroke volume measured by another technique (in this thesis: aortic flow probe or thermodilution).

Conductance catheter position

As can be appreciated from the theory behind the conductance technique, the catheter needs to lie straight (so that it lies perpendicular to the electric field), with its tip in the apex (so it does not 'miss' volume) and in the middle of the ventricle (so that it has equal sensitivity for the whole cylinder it measures). To achieve such a position in the left ventricle, two routes are followed in this thesis. One is the retrograde catheterization across the aortic valve. During surgery the antegrade catheterization via the pulmonary vein is usually easier and sometimes the only option, like in the aortic stenosis patients.

1.4 Pressure-volume loops in cardiac surgery

1.4.1 Requirements

If pressure-volume loops are to be measured during cardiac surgery, the method of choice is the conductance catheter which has procedural and technical benefits over other techniques (see previous section). A number of requirements must be met to be able to perform this measurement.

First of all, a conductance catheter needs to be positioned in the ventricle of interest. During surgery this can be done by

a) retrograde catheterization either via a distal systemic artery[55], the aortic root[60], the right ventricular outflow tract[61] or the pulmonary artery[62],
b) antegrade catheterization via the pulmonary vein[33,48] or a systemic vein[39] or
c) by apical puncture[63].

To check the correct position of the catheter, trans-esophageal echocardiography or fluoroscopy is used.

If a conductance catheter is placed, uncalibrated volume measurements are immediately available. In some cases (e.g. biventricular pacing) uncalibrated volume measurements are sufficient as only relative changes in long axis synchrony or stroke volume are of interest. However, as discussed in section 1.3.2, for absolute volume measurements a calibration procedure must be performed. This requires a measurement of blood resistivity (which may vary considerably during surgery[64]), a reference stroke volume or cardiac output measure (usually with a Swan-Ganz thermodilution catheter) and a hypertonic saline injection to determine parallel conductance. The hypertonic saline is injected either in the right atrium or pulmonary artery[56], or via a systemic vein[39,65].

Finally, a preload reduction is often performed to get the all-important load-independent indices of cardiac function (see section 1.2.2). During surgery the inferior caval vein is usually banded.

1.4.2 Overview of cardiac surgery studies

The application of pressure-volume loops in cardiac surgery has been rather limited[66]. A few notable exceptions are discussed in this section.

Operative care

Cardiac surgery is meant to treat heart disease, but to be able to perform the operation a number of procedures are necessary that result in a depression of ventricular function (e.g. ischemia), for which a number of protecting countermeasures are employed (e.g. cardioplegia). Pressure-volume loops have been used to study the impact and relative merits of various surgical procedures. These include studies into cardioplegia[32,38,67], the right ventricle during surgery[61], hypothermia[60], ultrafiltration[68], surgery for congenital heart disease[63,69] and ventricular function during valve operations[70].

Cardiomyoplasty

Cardiomyoplasty is the surgical procedure in which the latissimus dorsi muscle is wrapped around the failing, dilated heart to increase its contractility. Pressure-volume loops were useful to demonstrate the effects of this procedure on systolic and diastolic function[71-73].

Congenital heart disease

Congenital heart disease has an impact on cardiac function for which conventional diagnostic methods are sometimes less useful. Pressure-volume loops offer useful information on the right ventricle in congenital diseases such as transposition of the great arteries[74] and tetralogy of Fallot[75] and on the systemic ventricle in the Fontan procedure[76].

Ventricular remodeling

Surgical ventricular remodeling is a surgical treatment for heart failure patients with (very) dilated hearts. The procedure consists of the removal a piece of the left ventricle and subsequent ventricular reconstruction, thereby reducing ventricular size and improving its function. Pressure-volume loops have been used in these patients to study the systolic and diastolic performance of the heart after the Batista procedure[77-80] and after aneurysmectomy[81,82].

1.5 Aim and outline of the thesis

The subject of this thesis is the application of pressure-volume loops by conductance catheter in cardiac surgery. So the central theme is not a disease nor treatment but a diagnostic modality. Furthermore, the modality as such is not new; it has been extensively validated. However, despite the increasing experimental and clinical use of pressure-volume loops by conductance catheter in other areas like physiology and cardiology, few studies have been conducted in the field of cardiac surgery.
It is the aim of this thesis to describe the use of the conductance catheter technique in typical cardiac surgery subjects: valvular disease, coronary artery bypass grafting and mechanical support. Pressure-volume loops offer specific insights which no other diagnostic modality can offer and which can contribute to the correct diagnosis and useful treatment of patients. This thesis should contribute to the wider use of pressure-volume loops in general and the conductance catheter in cardiac surgery in particular.

Valvular disease

Aortic stenosis is a disease which leads to left ventricular hypertrophy, diastolic dysfunction, systolic dysfunction and eventually overt heart failure. Therefore, in patients having severe and symptomatic aortic stenosis, aortic valve replacement is recommended. However, a significant percentage of these patients do not show improvement of function or regression of hypertrophy. It is our hypothesis that these symptomatic patients have been operated too late. On the other hand aortic valve replacement in asymptomatic patients has inconsistent results and is not recommended[83]. This has lead to the hypothesis that in some patients symptoms develop after left ventricular dysfunction has become irreversible. In Chapter 2 *"Aortic stenosis"*, pressure-volume loops are used to determine in detail the systolic and diastolic function of the left ventricle. The goal of this ongoing study, is to identify prognostically important indices for the regression of hypertrophy and the normalization of left ventricular function after aortic valve replacement.

Apart from valvular stenosis, valvular leakage (regurgitation) also affects ventricular function. This raises a fundamental question, which has not been answered before: Can we diagnose aortic regurgitation in a pressure-volume loop? Conceptually, one would expect to detect aortic regurgitation as an increase in volume in the relaxation phase of the loop. Chapter 3 *"Aortic regurgitation"* discusses this concept but shows disappointing results: no correlation was found between the volume increase in the relaxation phase and the severity of aortic regurgitation determined by echocardiography.

Off-pump coronary artery bypass grafting

Conventional coronary artery bypass grafting is performed on the arrested heart with the aid of the cardiopulmonary bypass. It has been demonstrated that beating heart or off-pump coronary artery bypass grafting (OPCAB) can be performed safely with good results[84]. This advancement is due to the introduction of tissue stabilizers such as the Octopus[85]. Besides tissue stabilization for the anastamosis, the Octopus can also be used as a cardiac positioning device thereby allowing grafting of vessels on the posterior and inferior wall. However, performing OPCAB to these vessels is limited by hemodynamic instability that results from tilting the heart in order to reach the posterior and inferior wall of the left ventricle[86].

Chapter 4 *"Cardiac tilting"* is a study in which pressure-volume loops proved that the right ventricle is the problem during tilting of the heart with an Octopus. As soon as the right ventricle emerged as the problem during tilting, various types of right or bi-ventricular support devices have been suggested[87]. Chapter 5 *"Right ventricular support"* describes in detail one of such devices: the Enabler.

The identification of the right ventricle as the cause of the hemodynamic deterioration, has led to a change in strategy. Nowadays the Octopus is only used to stabilize the anastomosis site, while pericardial sutures or apical suction devices are used to position the heart with much better hemodynamic results[88,89]. This change in strategy has also limited the need for right ventricular support and currently only two devices are marketed as such[90,91].

Mechanical Support

Mechanical support is indicated when the heart can not pump enough blood to sustain viable circulation, in spite of maximum medical treatment[92,93]. This can occur during myocarditis, after acute and large myocardial infarction, acute mitral regurgitation, post-cardiotomy and acute worsening of chronic heart failure. Currently, two methods of circulatory support are widely used: The first is the intra-aortic balloon pump (IABP)[94], the second is an assist device placed either via a thoracotomy[95] or via the femoral vessels[96]. While the IABP is minimally invasive, it has limited capacity to support the heart. By contrast, assist devices are all very invasive and have numerous complications, but have excellent unloading and supporting characteristics. A minimal invasive device with better supporting characteristics than the IABP would be very useful in cardiac surgery.

In this thesis two chapters deal with mechanical support in an animal model of acute mitral regurgitation. In Chapter 6 "*Intra Aortic Balloon Pump in acute mitral regurgitation*" pressure-volume loops are used to show that the IABP does not support the left ventricle but does have a positive effect on the cardiac output by reducing mitral regurgitation.

Chapter 7 "*Propeller pump versus Intra Aortic Balloon Pump*" compares a new intra aortic propeller pump with the IABP. Hemodynamic measurements including pressure-volume loops showed that the new pump does have a small unloading effect on the left ventricle, but that it does not increase cardiac output and may have a negative effect on the perfusion of the heart and brain.

In the final chapter 8 "*Future pressure-volume loops in cardiac surgery*", an attempt is made to predict which future cardiac surgical patients would benefit from pressure-volume analysis.

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Chapter 2

Aortic stenosis

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2.1 Abstract

Background
Pre-operative left ventricular function is the strongest predictor of outcome after valve replacement for aortic stenosis. Although pressure-volume analysis with the conductance catheter technique can provide detailed information on left ventricular systolic and diastolic function, this technique has not yet been used in aortic stenosis patients. This study examined the potential use of left ventricular function measurements using pressure-volume analysis with a conductance catheter during surgery for aortic stenosis.

Methods
In six patients with severe symptomatic aortic stenosis, a conductance catheter was placed under trans esophageal echocardiographic guidance in the left ventricle via the right superior pulmonary vein.

Results
The procedure was successful in all patients and lengthened the operation by less than 30 minutes with no increase in bypass or aortic cross-clamping time. Pressure-volume analysis showed that systolic function was normal in all patients (EF 42-59%, end-systolic elastance 1.6-4.5mmHg/ml) while diastolic dysfunction was found in all patients (Tau 32-96ms, LV end-diastolic pressure 7-42 mmHg, atrial kick 25-60%). After valve replacement, systolic function improved but diastolic function did not.

Conclusions
The conductance catheter placed via the pulmonary vein can determine left ventricular systolic and diastolic dysfunction in detail in an individual patient with aortic stenosis before and after valve replacement. The technique may be used to extend diagnostic data from less-invasive modalities and to determine prognosis in the individual patient.

2.2 Introduction

Analysis of left ventricular pressure-volume loops has been accepted as the gold standard to study left ventricular function[1-3]. With the introduction of the conductance catheter and by interventions such as preload reduction by caval vein occlusion[4], detailed and load-independent indices for systolic and diastolic function have been obtained in surgical patients at our institution[5-7] and by other investigators[8,9].

Pressure-volume analysis has rarely been used in aortic stenosis patients for mainly three reasons. First, retrograde catheterization through the stenotic valve is associated with a high complication rate[10]. Second, catheterization through the stenotic valve affects cardiac function, probably by decreasing the aortic valve area[11]. Third, since the aortic valvular gradient and area are still the diagnostic hallmarks for clinical decision making and can be easily obtained by echocardiography, there has been no need for invasive diagnostics. However, timing of aortic valve replacement solely based on the severity of the gradient and symptoms can be disputed: The state of myocardial adaptation to chronic pressure volume overload is also prognostically relevant[12-14]. Consequently, a number of patients do not show regression of left ventricular hypertrophy and develop heart failure despite aortic valve replacement.

Pressure-volume analysis in aortic stenosis patients has been limited to radionuclide angiocardiography or ventriculography using a transseptal approach[15-18], and some investigators reported successful retrograde catheterization studies[19,20]. However, no study has reported the use of the conductance catheter in these patients although it has clear advantages (continuous volume and pressure measurement, beat-to-beat interventions, relative ease of use) compared to the previously applied methods.

It has been shown by our institution and other investigators that the conductance catheter can be placed via the pulmonary vein in surgical patients[7,9]. In this study we tested the feasibility of measuring pressure-volume loops in patients with aortic stenosis by inserting a conductance catheter in the left ventricle via the pulmonary vein before and after aortic valve replacement surgery.

2.3 Methods

2.3.1 Patient population

Six male patients (age 60-76 years) with symptomatic severe aortic valve stenosis (AVA < 1.0 cm^2)[21], were operated on for aortic valve replacement (Table 2-1). All patients had severely calcified, in origin tricuspid, aortic valves resulting in a significant gradient (42-90 mmHg) and increased left ventricular mass (122-160 g m^{-2}). Aortic regurgitation existed in one patient (nr. 3) but echocardiography could not detect any other important valve disease (grade 1 or less). Two types of mechanical valves were used for the replacement and patient nr. 4 had simultaneous bypass surgery of the right coronary artery. All patients gave informed consent and the study was approved on February 15, 1998 by the institutional review committee.

2.3.2 Intraoperative Patient Management

The anesthetic technique was standardized (total intravenous anesthesia with propofol and an opioid). Intravenous fluids were administered to maintain cardiac filling pressures at their normal values (central venous pressure 8-14 mmHg and pulmonary capillary wedge pressure 8-16 mmHg). If hypotension occurred, defined as a mean arterial pressure below 60 mmHg, it was treated using standard hospital procedures: intravenous fluids and, when indicated, incremental intravenous doses of 2.5 mg epinefrin and a dobutamin infusion whenever cardiac index decreased below 2 l/min/m^2.

2.3.3 Instrumentation

Pressure-volume loops were obtained by placing a conductance catheter with an integrated pressure sensor (Sentron ANP-223N, Roden, the Netherlands) into the left ventricle through an 18Fr atrial vent catheter (Terumo, Ann Arbor, MI) which was placed via an incision in the right superior pulmonary vein. The conductance catheter was connected to a Leycom Sigma 5DF system (CD Leycom, Zoetermeer, the Netherlands), that was used in dual frequency mode .

For aortic pressure measurements, a pressure tip catheter (Sentron ANP-530N, Roden, the Netherlands) was placed in the aortic root, just above the aortic valve. Finally, a pulmonary artery thermodilution catheter (Baxter, Deerfield, IL) was used to determine cardiac output and calibrate the conductance catheter.

2.3.4 Measurement protocol

Measurements were performed before and 15 minutes after the successful weaning of cardiopulmonary bypass when the patient was hemodyna-

mically stable. To evaluate the atrial contribution to ventricular filling, the start of the atrial contraction was defined as 50ms after the P-wave on the ECG. The time constant of relaxation, Tau, was calculated by the method of Villari[18].

To estimate myocardial contractility, measurements were obtained during inferior caval vein occlusion which results in estimation of the slope Ees of the end-systolic pressure-volume relation (Figure 2-1)[4]. In two patients the occlusion produced ectopic beats, and Ees could not be determined pre-operatively. All measurements were done at end-expiration breath hold to eliminate the effect of ventilation on the conductance measurements.

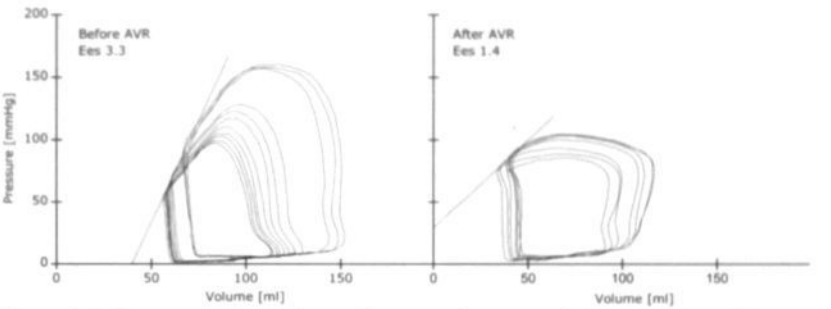

Figure 2-1: Pressure-volume loops during inferior caval vein occlusion (Patient 4) before (left) and after aortic valve replacement (right). The end-systolic pressure volume relation is drawn in. The slope of this relation, end systolic elastance Ees, is given in the upper left corner of each graph.

2.3.5 Conductance catheter position and calibration

The conductance catheter contains metal rings that can clearly be seen with ultrasound (Figure 2-2). Therefore, the correct position of the catheter, along the long axis of the ventricle with its pigtail in the apex, could be validated using trans-esophageal echocardiography. Care was taken to avoid catheter-wall contact and kinking or bending of the catheter.

The conductance catheter measures ventricular volume in five 1 cm-segments. With the pulmonary vein approach, the upper segments of the catheter may measure atrial volume instead of ventricular volume. Any atrial segments could easily be excluded by observing the volume segmental signals on the display of the conductance console: An atrial segment is out-of-phase with a ventricular segment as the atrium fills during systole and empties during diastole, exactly the opposite to a ventricular volume segment. An example of such an out-of-phase segment

is given in Figure 2-2. After achieving the correct position, measurements were immediately performed so no fixation of the catheter was necessary. Positioning of the conductance catheter took less than ten minutes in all patients. During aortic valve replacement the catheter was left in place, so no re-catheterization was necessary for the post-operative measurements. Conductance calibration in this open-heart setting was done in the standard manner by comparing conductance with thermodilution derived stroke volume[5]. Parallel conductance was determined by injecting 7.5ml 6.5% hypertonic saline into the pulmonary artery[5]. The average time necessary to perform all conductance measurements (incl. calibration) was 9 minutes (range 6-15) pre-operatively and 6 minutes (range 4-7) post-operatively.

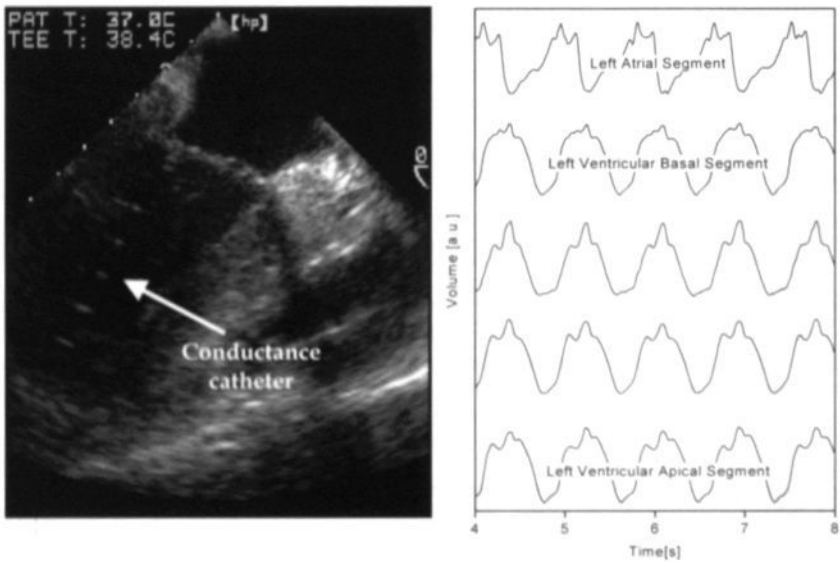

Figure 2-2: Left: TEE image of the conductance catheter inside the left ventricle. The metal rings on the conductance catheter can be clearly seen. Right: Volume segments of a conductance catheter correctly placed in the left ventricle. The ventricular long axis is too short to include all five volume segments, so only the bottom four segments are used to record ventricular volume. The top segment is an atrial volume segment and is out-of-phase with the ventricular segments as the atrium fills during systole and empties during diastole.

Table 2-1: Peri-operative patient characteristics

Patient	Age [y]	Weight [kg]	BSA [m^2]	LVMI [$g\ m^{-2}$]	AVA [cm^2]	Pre-op AI [grade]	Pre-op Gradient [mmHg]	Pre-op HR [bpm]	Pre-op MAP [mmHg]	XCL Time [min]	CPB Time [min]	Mechanical Valve	Post-op Gradient [mmHg]	Post-op HR [bpm]	Post-op MAP [mmHg]
1	60	73	1.81	151	0.7	1	42	70	68	79	140	Sorin Bicarbon 23	20	84	61
2	76	85	1.99	160	0.6	trace	61	77	89	79	110	Carbomedics 23	22	79	70
3	62	77	1.84	140	0.6	2/3	50	75	82	61	88	Carbomedics 23	5	73	94
4	71	75	1.85	139	0.6	1	69	66	68	97	124	Sorin Bicarbon 25	8	72	61
5	67	85	2.07	132	0.6	1	90	77	84	100	144	Sorin Bicarbon 25	9	84	91
6	64	80	1.98	122	0.4	1	82	84	67	74	90	Sorin Bicarbon 23	28	81	50

BSA: body surface area; LVMI: left ventricular mass index; AVA: aortic valve area (Gorlin formula); Pre-op AI: aortic insufficiency of the native valve determined by echocardiography; Pre-op Gradient: peak-to-peak gradient of the native valve; HR: Heart Rate; MAP: Mean Arterial Pressure; Mechanical valve: valve used for aortic valve replacement; Post-op Gradient: peak-to-peak gradient of the mechanical valve in situ; XCL: Cross-clamping; CPB: Cardiopulmonary Bypass

2.4 Results

The pressure-volume loops of all patients before and after aortic valve replacement, are given in Figure 2-3. Both the left ventricular pressure and the aortic pressure versus ventricular volume are plotted as this gives the best impression of both the gradient and the moment of valve opening and closure. Furthermore, the area of the curve between the aortic and the ventricular loop is the extra stroke work (39-59%, see Table 2-2) performed by the ventricle to overcome the stenosis. After implanting the mechanical valve, this extra work reduced markedly.

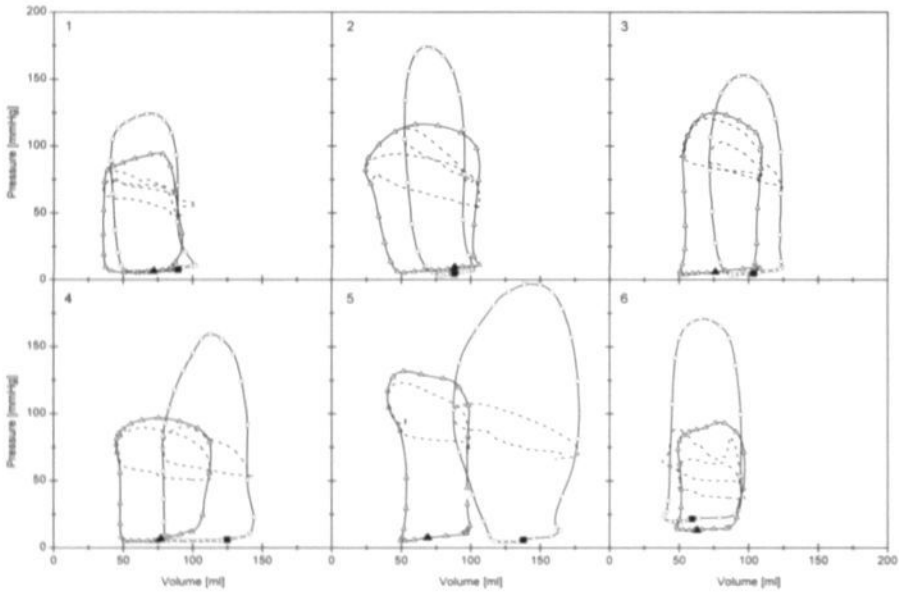

Figure 2-3: Pressure-volume loops before (-□-) and after (-Δ-) aortic valve replacement of patients with symptomatic aortic valve stenosis. Drawn in is the aortic pressure vs. ventricular volume (- -) as it gives a good impression of the gradient and the extra stroke work necessary to overcome the stenosis. The patient number, corresponding to the tables, is given in the upper left corner of each figure. To evaluate the atrial contribution to ventricular filling, a marker is placed at the start of the atrial contraction. Time between points is 28ms.

Table 2-2: Systolic function indices before and after aortic valve replacement for aortic stenosis

Patient	Contractility		Contraction				Ejection							
	Ees		[dP/dt]max		[(dP/dt)/P]max		EF		MNSER		SW		SWextra	
	[mmHg ml^{-1}]		[mmHg s^{-1}]		[sec^{-1}]		[%]		[sec^{-1}]		[g m]		[% of SW]	
Normal	2.8		1600		44		72		3.3		81			
Dysfunction	<1.0		<1000		<27		<40		<1.6		<35			
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	4.5	2.8	1014	1116	28	37	59	61	1.9	2.5	70	62	39	21
2	2.2	1	1291	1244	35	29	49	77	1.7	2.8	85	100	41	23
3	--	2.7	1232	1127	35	29	42	53	1.4	1.1	90	81	47	6
4	3.3	1.4	1604	1392	32	34	45	56	1.2	1.7	109	72	43	11
5	--	1.5	1711	1504	36	28	45	60	1.4	2.3	184	78	52	11
6	1.6	1.6	1776	1130	27	26	58	43	1.7	1.3	93	45	59	37
Average	2.9	1.8	1438	1252	32	31	50	58	1.6	2	105	73	45	18

Ees: slope of the ESPVR relation; [dP/dt]max: peak positive left ventricular pressure derivative; [(dP/dt)/P]max: pressure normalized peak positive left ventricular pressure derivative; EF: ejection fraction; MNSER: mean normalized systolic ejection rate; SW: stroke work; SWextra: extra work done to overcome the stenosis. Normal and dysfunction values are taken from[27]. Underlined values indicate systolic dysfunction.

2.4.1 Systolic function

Systolic function was unaffected pre-operatively in these aortic stenosis patients as shown by the indices in Table 2-2. The best index available for assessment of the contractility of the ventricle, end-systolic elastance Ees, was also in the normal range although this parameter strongly varied between patients. The isovolumic contraction and ejection indices were relatively low but did not reach abnormal values. After aortic valve replacement, the stroke work decreased and ejection indices improved (Table 2-2).

2.4.2 Diastolic function

In contrast to systolic function, all patients suffered from diastolic dysfunction as evidenced by the delayed relaxation (Table 2-3). In only two patients (nrs. 5 & 6) this led to a filling problem, with high end-diastolic pressure and reliance on the atrial kick for 50% or more of the end-diastolic volume. The compliance of the left ventricle varied between patients but was lower than in control subjects[3]. The end-diastolic pressure-volume relationship from which the compliances are calculated[3], are presented in Figure 2-4: Some patients (e.g. patient 5 and 6) show a decrease in compliance at higher end-diastolic volume which indicates that the ventricle is maximally stretched. After aortic valve replacement, atrial filling remained important and the delayed relaxation did not improve (Table 2-3).

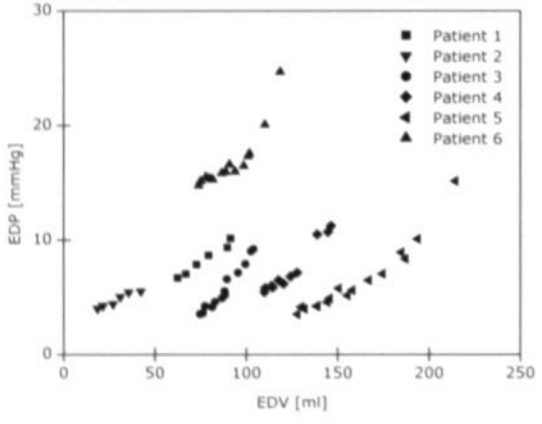

Figure 2-4: End diastolic pressure volume relations obtained during inferior caval vein occlusion. The slope of the curve determines the compliance of the chamber (see Table 2-3). Pre-operative data is given for all patients except patient 3 and 5.

Table 2-3: Diastolic function indices before and after aortic valve replacement for aortic stenosis

Patient	Relaxation						Filling									
	Tau		IVRT		$[dP/dt]_{min}$		LVEDP		PFR_{RFF}		E/A		AF		C_{DIA}	
	[ms]		[ms]		[mmHg s^{-1}]		[mmHg]		[ml s^{-1}]		[-]		[%]		[ml $mmHg^{-1}$]	
Dysfunction	>48		>105		<1100		>16		<160		<0.5					
Normal	36		84		1864		8		300		1.2		15		10	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	56	98	116	108	1145	999	12	8	435	424	2	1.7	25	29	8.7	6.4
2	63	93	127	110	1310	1071	7	11	250	284	1.6	1	36	27	9.1	14.1
3	61	63	120	144	1153	1370	8	8	243	267	0.9	0.5	44	58	--	5.1
4	96	73	128	116	813	1203	11	13	283	246	1.1	0.6	26	43	6.3	2.7
5	56	61	128	105	1310	1956	19	14	228	246	0.5	3.3	50	62	--	8.9
6	32	75	120	122	1853	908	24	15	203	168	0.3	0.5	60	59	5.9	6.3
Average	61	77	123	118	1264	1251	14	12	274	331	1.1	1.3	38	44	7.5	7.3

Tau: Time constant of isovolumic left ventricular pressure; IVRT: Isovolumic relaxation time, the time from aortic valve closure to mitral valve opening; $[dP/dt]_{min}$: Peak negative left ventricular pressure derivative; LVEDP: Left ventricular end-diastolic pressure; PFR_{RFF}: Peak filling rate during the early, rapid filling phase; E/A ratio: The ratio of PFR_{RFF} and PFR during atrial contraction; AF: Percentage of end-diastolic volume resulting after atrial contraction. C_{DIA}: Diastolic chamber compliance[3]. Normal and dysfunction values taken from[28]. Underlined values indicate diastolic dysfunction.

2.4.3 Intra-operative hemodynamic management

As can be seen in Table 2-1, filling pressures were maintained within normal limits in all patients, weaning from bypass was uneventful in all patients and no patient required inotropic support. Mean arterial pressure and heart rate were recorded to compare pre- and post-operative hemodynamic state. In all these were similar, except in patient 6 who experienced a decline in mean arterial pressure of more than 25% after valve replacement.

2.5 Discussion

2.5.1 Pressure-volume analysis in aortic stenosis patients

In this study, we presented a new method to perform pressure volume-analysis in patients with aortic stenosis during surgery for aortic valve replacement. We placed a conductance catheter via the right superior pulmonary vein and advanced it to the correct position in the left ventricle under echocardiographic guidance and by checking the volumetric segments of the conductance catheter[7,9].
The procedure, including catheter placement, calibration and measurements before and after aortic valve replacement, lengthened the operation by less than 30 minutes with no increase in bypass or cross clamping time.

There are clear benefits from the two other proposed methods to record pressure-volume loops in these patients i.e. ventriculography and radionuclide angiocardiography. Both have the drawback that they can only sample every 20ms and do not measure beat-to-beat ventricular volume. This limits their ability to determine load-independent measures of systolic and diastolic function as preload manipulation by caval vein occlusion is impossible (during surgery this problem can be overcome by using the cardiopulmonary bypass to reach a certain reduction of preload by withdrawal of blood[17]). Furthermore, both methods still require catheterization for the pressure measurement by the transseptal or retrograde approach which entails risk[10].

The method proposed in this study does not have these limitations. It only requires pulmonary vein catheterization and measures volume and pressure continuously. The pulmonary vein catheterization is a routine procedure for any cardiac surgeon and is similar to introducing a left ventricular vent. Preload manipulation by external caval vein occlusion (Figure 2-1) was successful in 10 of 12 cases, with the only problem being extra systolic beats.
It was observed that these extra systolic beats tended to occur during caval vein occlusion but not so much when the occlusion was released. It may be possible to determine the end-systolic and diastolic pressure volume relation by performing measurements during the release of the occlusion (which was not done in this study).

The main drawback of the proposed method is that it can only be performed during surgery. The same holds for ventriculography and radionuclide cardiography if load independent indices need to be determined[17]. At present, this excludes the use of pressure-volume loops as

a pre-operative diagnostic tool in the decision making for aortic valve replacement. In future, it may be possible to obtain pre-operative pressure-volume loops with new techniques such as transthoracic conductance[22] or echocardiography[23] in combination with a very small pressure catheter, but these methods have not yet been extensively validated.
However, pressure-volume loops may be of value to confirm pre-operative diagnostic methods and may be used to determine the prognosis and post-operative treatment of the individual patient as pre-operative systolic and diastolic dysfunction are the most powerful predictors of outcome after valve replacement[13,14].

2.5.2 Pressure-volume analysis in the individual patient

In this highly selective group of aortic valve stenosis patients, systolic function is not affected, and none of the patients are in heart failure as evidenced by the high Ees compared to heart failure patients[24]. In contrast, diastolic dysfunction is present in all patients and two have a filling problem which can eventually lead to diastolic heart failure[21]. So, if the natural history of the disease is first left ventricular hypertrophy, then diastolic dysfunction, then systolic dysfunction and finally heart failure[13], all these patients can be ranked in a state between diastolic and systolic ventricular dysfunction.

2.5.3 Systolic and diastolic function

Systolic function, represented by the ejection and contraction phase, is preserved in these aortic stenosis patients, although in the low-normal range. The ejection phase is primarily affected because the ventricle has to eject through the stenotic valve. Thus, ejection fraction and the related index mean normalized systolic ejection rate are decreased before the valve replacement but improve immediately after the new valve is placed.
The cardiac muscle itself is not affected as seen by the normal contraction phase and contractility index Ees, which shows that none of the patients were in systolic heart failure. The ventricle can therefore still perform the extremely high stroke work, of which almost half is used to overcome the stenosis. After the valve replacement, the contractility seems to decrease somewhat. It is known that the cardiopulmonary bypass has a negative influence on the contractility of the right ventricle[25] and the observed decrease in left ventricular contractility may have a similar cause.

In contrast, the pressure-volume analysis clearly confirms that diastolic dysfunction is present in all aortic stenosis patients as relaxation is delayed and patients rely heavily on the atrial kick for their filling[13,15]. Furthermore, Fig. 2-5 and Table 2-3 illustrate that left ventricular compliance is decreased which is known to be caused by the increased stiffness due to hyper-

trophy[16]. Fig. 2-5 also shows that in some patients (e.g. patient 5 and 6) compliance increases strongly when preload is reduced, indicating that these patients have minimal preload-reserve.
The varying degree of diastolic dysfunction between aortic stenosis patients has been observed by other investigators[15] and is important for the prognosis of the individual patient[13]. The diastolic dysfunction is known to be caused by hypertrophy and it does not improve immediately after aortic valve replacement[18].

2.5.4 Clinical relevance

This study shows that a single conductance measurement can provide the clinician several load independent indices of systolic and diastolic function in the individual patient with aortic stenosis. In our opinion catheterization through the stenotic aortic valve is currently not indicated in the symptomatic patient with severe aortic stenosis. However, we can envisage that the technique may be of use in the timing of aortic valve replacement in asymptomatic patients and in patients with moderate stenosis. In these patients, the quantitative diagnosis of heart failure and diastolic dysfunction is limited with non-invasive modalities such as echocardiography especially in the presence of normal systolic function[26]. The conductance method may then be used to validate and extend the accuracy of echocardiographic data. Finally, this study again shows that intra-operative conductance measurements are feasible and relatively easy and quick to perform, possibly expanding its use to other interventions in the setting of open heart surgery.

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Chapter 3

Aortic regurgitation

Submitted for publication as:
Dekker ALAJ, Barenbrug PJC, van der Nagel T, van der Veen FH, Maessen JG. Diagnosis of aortic regurgitation with pressure-volume loops.

3.1 Abstract

Background
Calibration of pressure-volume loops via a conductance catheter requires knowledge of left ventricular stroke volume. Usually this stroke volume is derived by thermodilution, but this method underestimates left ventricular stroke volume if aortic regurgitation is present. The presence and severity of aortic regurgitation might be determined in a pressure-volume loop itself as a volume increase in the relaxation phase. This hypothesis is tested in a comparative study with echocardiography in patients.

Methods
In 36 consecutive patients (26 aortic stenosis; 10 heart failure) with aortic regurgitation ranging from none to severe, pressure-volume loops were obtained during surgery and compared to echocardiography. Aortic regurgitation was quantified from the pressure-volume loops as the volume increase during relaxation. The relaxation phase was defined as starting at dP/dt_{min} or minimal left ventricular volume, and ending at minimal left ventricular pressure or the moment where left ventricular pressure declines below end-diastolic pressure.

Results
No correlation could be found between the degree of aortic regurgitation by echocardiography and the quantification of aortic regurgitation via pressure-volume loops. However, the amount of aortic regurgitation measured with pressure-volume loops decreased significantly after aortic valve replacement.

Conclusions
The increase in left ventricular volume during the relaxation phase of a pressure-volume loop does not correlate with the severity of aortic regurgitation. Therefore, aortic regurgitation cannot be quantified in a pressure-volume loop and should be quantified by other methods when calibration of the conductance catheter is done with thermodilution.

3.2 Introduction

Analysis of left ventricular pressure-volume loops (PV-loops) is the gold standard to study left ventricular function[1-3]. With the introduction of the conductance catheter[4], the measurement of beat-to-beat PV-loops became feasible and since then, we and others have successfully applied this technique in surgical patients[5-9].

The conductance catheter is calibrated by comparing conductance derived left ventricular stroke volume to the stroke volume measured via thermodilution[4]. However, if severe valvular regurgitation is present, the left ventricular stroke volume is much higher than thermodilution derived stroke volume. Ignoring this difference and calibrating the conductance catheter with thermodilution, will lead to an underestimation of the absolute volume value if valvular regurgitation is present. Valvular regurgitation is usually determined by echocardiography[10] but in light of the above it would also be beneficial to detect valvular regurgitation in a pressure-volume loop.

The corners of a pressure-volume loop are determined by valvular opening and closure (Figure 3-1). For instance, it can be assumed that aortic regurgitation is visible as an increase of volume in the relaxation phase, and that the amount of volume increase in that phase is related to the amount of valvular regurgitation. However, studies on aortic regurgitation with PV-loops have not yet been reported.

In this study, we test the hypothesis that aortic regurgitation can be diagnosed in a pressure-volume loop as an increase in volume in the relaxation phase. It is the goal of this study to compare this new method of detecting aortic regurgitation with echocardiography.

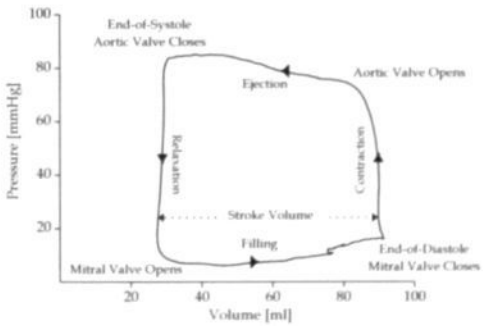

Figure 3-1: A normal left ventricular pressure-volume loop

3.3 Methods

3.3.1 Patients and Anesthesia

In this retrospective study, thirty-six patients were included with the only criteria being the availability of both PV-loops and echocardiographic data. In twenty-six patients, PV-loops were recorded during surgery for aortic valve replacement due to symptomatic aortic valve stenosis. In ten patients with heart failure and left bundle branch block, PV-loops were recorded during surgery for epicardial left ventricular pacing lead placement. A trans-thoracic echocardiography (Doppler color flow mapping and vena contracta imaging) was performed in all patients as part of the normal clinical evaluation before surgery. The aortic regurgitation was graded none, mild, moderate or severe, and was used as a gold standard to compare to aortic regurgitation detection with PV-loops.

The anesthetic technique was standardized (total intravenous anesthesia with propofol and an opioid). Intravenous fluids were administered to maintain cardiac filling pressures at their normal values (central venous pressure 8-14 mmHg and pulmonary capillary wedge pressure 8-16 mmHg). If hypotension occurred, defined as a mean arterial pressure below 60 mmHg, it was treated using standard hospital procedures: intravenous fluids and, when indicated, incremental intravenous doses of 2.5 mg epinefrin and a dobutamin infusion whenever cardiac index decreased below 2 l/min/m^2.

3.3.2 Conductance catheter

In the aortic stenosis patients, PV-loops were obtained by placing a conductance catheter (CDLeycom, Zoetermeer, The Netherlands) into the left ventricle through an 18Fr atrial vent catheter (Terumo, Ann Arbor, MI) which was placed via an incision in the right superior pulmonary vein. In the heart failure patients, the conductance catheter was placed via the femoral artery under fluoroscopy. The conductance catheter was connected to a CDLeycom CFL conductance system (CDLeycom, Zoetermeer, The Netherlands).

3.3.3 Relaxation phase definition

It is the hypothesis of this study that aortic regurgitation is visible as an increase in ventricular volume in the (usually isovolumic) relaxation phase. This phase can be said to begin at aortic valve closure and to end at mitral valve opening. However, aortic valve closure and mitral valve opening are not always evident in a pressure-volume loop. To overcome this problem, we used the following four definitions for the relaxation phase:

1. From maximum negative left ventricular pressure derivative ($dPdt_{min}$) to minimal left ventricular pressure (LVP_{min})
2. From maximum negative left ventricular pressure derivative ($dPdt_{min}$) to the point were left ventricular pressure declines below left ventricular end-diastolic pressure (LVP<EDP).
3. From minimal left ventricular volume (LVV_{min}) to minimal left ventricular pressure (LVP_{min})
4. From minimal left ventricular volume (LVV_{min}) to the point were left ventricular pressure declines below left ventricular end-diastolic pressure (LVP<EDP).

All these points are readily detected in a pressure-volume measurement and will be operator-independent.

3.3.4 Quantification of aortic regurgitation in PV-loops

With these definitions of the relaxation phase, the amount of aortic regurgitation in that phase can be quantified as the left ventricular volume at the end of the relaxation phase minus the volume at the start of the phase divided by the stroke volume. Thus defined, this "regurgitant fraction" indicates how much blood enters the ventricle in the relaxation phase as a fraction of the total stroke volume. With the aforementioned four definitions of the relaxation phase, four values of the regurgitant fraction are obtained.

3.3.5 Statistical Analysis

Measurements done before and after aortic valve replacement were compared via a paired t-test. Significance was assumed if the p-value was less than 0.05.

3.4 Results

Patient data are summarized in Table 3-1 and Figure 3-2. There was no correlation between echocardiography and any of the PV-loops derived indices for aortic regurgitation. In the aortic stenosis patients that had PV-loops derived aortic regurgitation of 5% or more before the aortic valve replacement, this regurgitation reduced significantly after the aortic valve was replaced (Figure 3-3).

Table 3-1: Aortic regurgitation by echocardiography and pressure-volume loops

Patient	Primary Disease	AR_{ECHO} [grade]	AR_1 [%SV]	AR_2 [%SV]	AR_3 [%SV]	AR_4 [%SV]
1	Heart Failure	none	0	0	5	0
2	Heart Failure	none	0	0	5	11
3	Aortic Stenosis	none	0	0	25	0
4	Aortic Stenosis	none	7	3	7	3
5	Aortic Stenosis	none	12	0	16	3
6	Aortic Stenosis	none	14	5	15	6
7	Heart Failure	none	15	6	17	9
8	Aortic Stenosis	none	15	49	20	50
9	Heart Failure	none	25	0	35	1
10	Heart Failure	none	50	22	50	32
11	Heart Failure	trace	37	5	41	9
12	Aortic Stenosis	trace	40	30	47	38
13	Heart Failure	mild	3	2	4	3
14	Aortic Stenosis	mild	5	5	6	6
15	Aortic Stenosis	mild	7	0	17	1
16	Aortic Stenosis	mild	7	4	11	7
17	Aortic Stenosis	mild	10	6	12	7
18	Heart Failure	mild	12	6	15	9
19	Aortic Stenosis	mild	36	24	37	25
20	Aortic Stenosis	mild	37	9	41	13
21	Aortic Stenosis	mild	37	12	40	15
22	Aortic Stenosis	mild	50	24	50	29
23	Aortic Stenosis	mild to moderate	13	0	23	8
24	Aortic Stenosis	mild to moderate	15	3	15	4
25	Aortic Stenosis	mild to moderate	18	0	30	0
26	Aortic Stenosis	mild to moderate	19	11	23	16
27	Aortic Stenosis	mild to moderate	26	0	33	0
28	Aortic Stenosis	mild to moderate	39	9	40	10
29	Aortic Stenosis	moderate	0	0	4	0
30	Aortic Stenosis	moderate	20	4	26	10
31	Aortic Stenosis	moderate	48	7	50	9
32	Aortic Stenosis	moderate	50	50	50	50
33	Aortic Stenosis	moderate to severe	0	0	8	0
34	Heart Failure	moderate to severe	21	10	24	14
35	Heart Failure	moderate to severe	27	17	29	18
36	Aortic Stenosis	moderate to severe	32	12	34	15

AR_{ECHO}: Aortic regurgitation determined by echocardiography; AR_1: Left ventricular volume increase from dP/dt_{min} to LVP_{min}; AR_2: Left ventricular volume increase from dP/dt_{min} to the moment were $LVP<LVP_{ED}$; AR_3: Left ventricular volume increase from LVV_{min} to LVP_{min}; AR_4: Left ventricular volume increase from LVV_{min} to the moment were $LVP<LVP_{ED}$; SV: Stroke volume

3.5 Discussion

It was the aim of this study to assess whether aortic regurgitation can be detected in PV-loops obtained with a conductance catheter. The hypothesis was that aortic regurgitation would manifest itself in PV-loops as a left ventricular volume increase in the relaxation phase. The results of this study are disappointing: No correlation was found between echocardiography and PV-loops in the quantification of aortic regurgitation. However, in the subset of patients that underwent an aortic valve replacement, significantly less volume increase was seen in the relaxation phase after the valve was replaced. A number of explanations are possible for these observations.

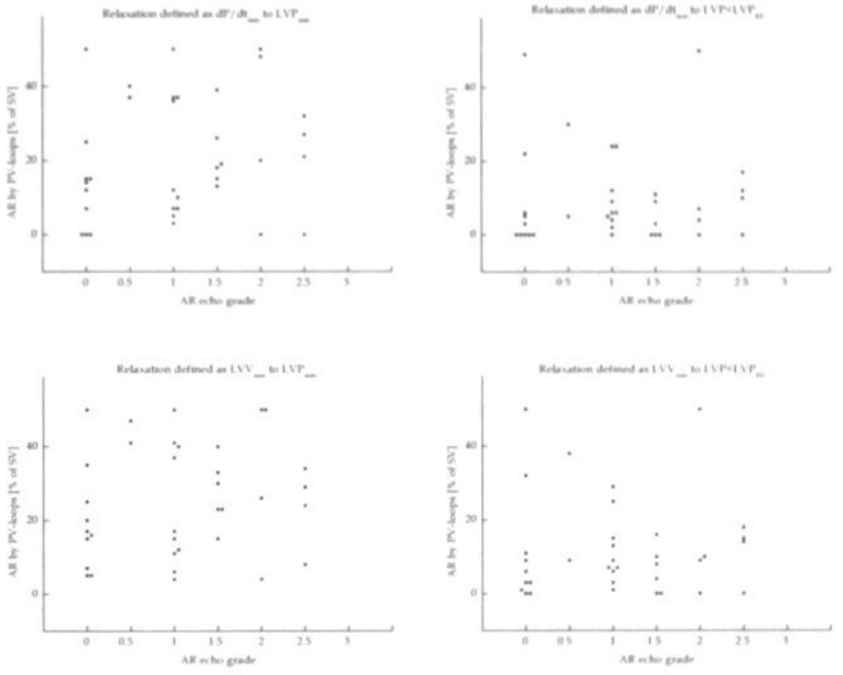

Figure 3-2: Comparison of the diagnosis aortic regurgitation by echocardiography and by pressure-volume loops in 36 patients. Aortic regurgitation is quantified by pressure-volume loops as the volume increase during the relaxation phase as a percentage of the stroke volume. The relaxation phase is defined as (see also Methods section): Top left: from $dPdt_{min}$ to LVP_{min}; Top right: from $dPdt_{min}$ to LVP<EDP; Bottom left: from LVV_{min} to LVP_{min}; Bottom right: from LVV_{min} to LVP<EDP.
Echo grading of aortic regurgitation: 0=none, 0.5=trace, 1=mild, 1.5=mild to moderate, 2=moderate, 2.5=moderate to severe, 3=severe.

3.5.1 Aortic regurgitation: A holo-diastolic disease

The severity of aortic regurgitation depends on the pressure gradient and the regurgitant orifice area[11]. The pressure gradient across the valve increases rapidly in the relaxation phase but stays fairly constant for the remainder of diastole. On the other hand, the regurgitant orifice may also depend on the pressure gradient and thus may increase, decrease or remain constant during the relaxation phase and the rest of diastole[11,12]. For instance, if the regurgitant orifice becomes smaller at high pressure gradients than much more regurgitation occurs in the relaxation phase compared to the situation were the regurgitant orifice increases with the pressure gradient.

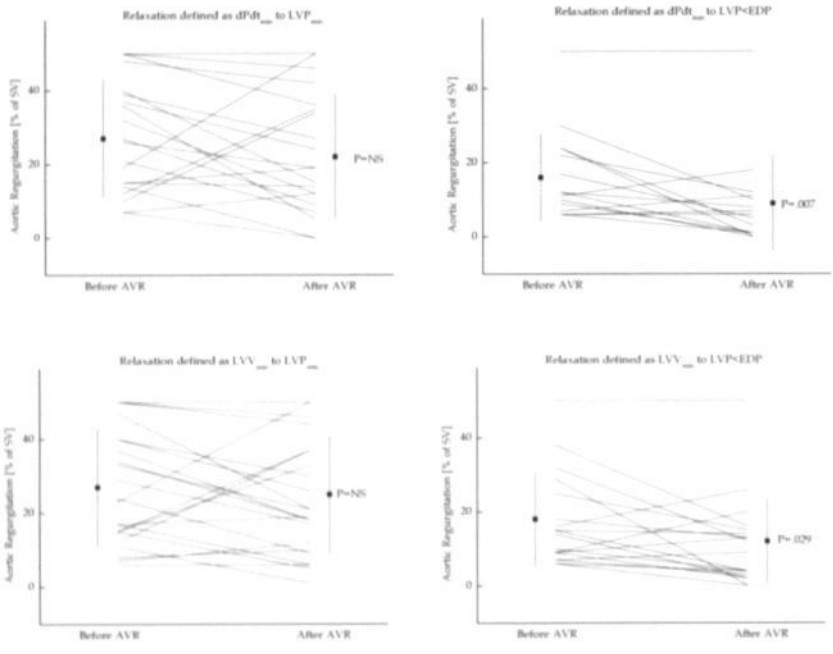

Figure 3-3: Aortic regurgitation with pressure-volume loops before and after AVR in patients with pre-AVR aortic regurgitation of 5% or more. Aortic regurgitation is quantified by pressure-volume loops as the volume increase during the relaxation phase as a percentage of the stroke volume. The relaxation phase is defined as (see also Methods section):
Top left: from dP/dt_{min} to LVP_{min}; Top right: from $dPdt_{min}$ to $LVP<LVP_{ED}$; Bottom left: from LVV_{min} to LVP_{min}; Bottom right: from LVV_{min} to $LVP<LVP_{ED}$.

In light of the above, it is important to realize that echocardiography and PV-loops measure a different variable at different time points during diastole. With echocardiography, the peak regurgitant jet in diastole is

measured. In the proposed PV-loops method however, the volume increase during the relaxation phase is taken as a measure for aortic regurgitation. This difference in variable and timepoint may explain the bad correlation between echocardiography and PV-loops despite the observed decrease in aortic regurgitation in the relaxation phase upon valve replacement

3.5.2 Definition of the relaxation phase

The method proposed in this study to quantify aortic regurgitation in a pressure-volume loop, depends on the correct identification of the relaxation phase. The (usually isovolumic) relaxation phase is defined as starting at aortic valve closure and ending at mitral valve opening. Both are not always evident in a pressure-volume loop. As a substitute, we used dP/dt_{min} and LVV_{min} as starting points, and LVP_{min} and $LVP<LVP_{ED}$ as end-points of the relaxation phase. Especially the latter two are questionable. For instance, other investigators have shown that minimal left ventricular pressure sometimes occurs long after the mitral valve is open, leading to a 20% mean volume increase in the relaxation phase, although that study did not exclude the presence of aortic regurgitation[13]. Delayed relaxation, which is often encountered in aortic stenosis patients, will lead to an even later occurrence of minimal left ventricular pressure. This is a possible explanation why a relaxation phase definition incorporating LVP_{min} leads to such a wide variation in values of aortic regurgitation (Figure 3-2 and Figure 3-3). The definition of the relaxation phase from dP/dt_{min} to $LVP<LVP_{ED}$ seems to be more appropriate based on our results (Figure 3-3).

3.5.3 Aortic regurgitation due to the conductance catheter

In the heart failure patients that were catheterized retrogradely, some additional aortic regurgitation may result from the presence of the conductance catheter across the aortic valve. However, whether this produces some non-physiological regurgitation, is still a matter of debate[14].

3.5.4 Calibration of the conductance catheter in aortic regurgitation

Calibration of the conductance catheter depends on the correct identification of LV stroke volume. In aortic regurgitation patients, LV stroke volume can be determined by measuring forward stroke volume via thermodilution and by using echocardiography to determine the regurgitant fraction[15,16]. If regurgitant fraction and net stroke volume are known, then total left ventricular stroke volume can be calculated and used to calibrate the conductance catheter.

3.5.5 Study limitations

In this retrospective analysis patients were studied that had specific diseases and do not represent the general patient population. More

specifically, it can not be excluded that coexistence of aortic regurgitation with heart failure and aortic stenosis results in a variety of hemodynamic dysfunctions that may have influenced these results.

3.5.6 Conclusion

The increase in left ventricular volume during the relaxation phase of a pressure-volume loop does not correlate with the severity of aortic regurgitation. Therefore, aortic regurgitation can not be quantified in a pressure-volume and should be quantified by other methods when calibration of the conductance catheter is done with thermodilution.

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Chapter 4

Cardiac tilting

Published as:

Dekker AL, Geskes GG, Cramers AA, Dassen WR, Maessen JG, Prenger KB, van der Veen FH. Right ventricular support for off-pump coronary artery bypass grafting studied with bi-ventricular pressure-volume loops in sheep. Eur J Cardiothorac Surg 2001;19:179-184.

4.1 Abstract

Objectives
Tilting the heart during off-pump coronary artery bypass grafting (OPCABG) causes a strong decrease in cardiac output. It is hypothesized that this decrease is caused by reduced right ventricular filling and that right ventricular support is thus the best way to restore cardiac output. Simultaneous left and right ventricular pressure-volume loops were used to test this hypothesis.

Methods
In seven sheep, the heart was tilted with the use of an Octopus device. After unsupported tilting, a novel right ventricular support, the Enabler, was activated at a pulsatile flow of 1.6 l/min. Pressure-volume loops of both ventricles were obtained using conductance catheters, and cardiac output was monitored with an aortic flow probe.

Results
Tilting reduced cardiac output by 31% (4.4-3.1 l/min, P=0.001) and right ventricular end-diastolic volume by 44% (86-51 ml, P=0.005), while right ventricular end-diastolic pressure did not decrease. Left ventricular systolic pressure was not significantly reduced upon tilting and even increased in two animals. During Enabler right ventricular support, the cardiac output remained 23% lower than pre-tilting values (3.4 vs. 4.4 l/min, P=0.001).

Conclusions
Restricted right ventricular filling is the primary cause of the strong decrease in cardiac output during tilting. The Enabler right ventricular support can currently not restore cardiac output to pre-tilting values, mainly caused by its limited output and a decrease in right ventricular output upon Enabler activation. Constant monitoring of cardiac output is crucial during (unsupported or supported) tilting as blood pressure alone may not reflect the extent of the reduction in cardiac function.

4.2 Introduction

Left ventricular pressure-volume loops measured by a conductance catheter are now commonly used to measure the effect of disease, new drugs, left heart assist and cardiomyoplasty on left ventricular function[1-5]. Right ventricular pressure.volume loops are less often used[6,7], but also show good correlation with other techniques[8].

Simultaneous left and right ventricular pressure-volume loops are necessary for an in-depth investigation of cardiac function, especially when studying interventions that affect both ventricles. One such intervention is cardiac tilting for multivessel off-pump coronary artery bypass grafting (OPCABG)[9,10].
OPCABG eliminates the use of the extracorporeal circulation with its well-known complications[11]. In this procedure, the Octopus device (Medtronic Inc., Minneapolis, MI) is often used to stabilize the site of the anastomosis, but can also be used to lift and rotate the heart, thereby allowing multivessel OPCABG[12]. However, this so-called cardiac tilting is not without hemodynamic consequences; tilting the heart is reported to cause a 44% decrease in stroke volume in healthy pigs and to reduce systemic blood pressures with a concomitant higher right atrial pressure, suggesting right ventricular dysfunction[9,10]. The hemodynamic consequences of cardiac tilting limit the use of OPCABG in patients with poor cardiac function.

The Enabler (Hemodynamics Systems Ltd., Yoqneam, Israel) was developed to support the right ventricle during cardiac tilting, thereby making multivessel OPCABG possible in all patients. It consists of a 24F catheter that is placed via surgical preparation of the femoral vein or via the right atrium and creates a pulsatile flow, 1:1 triggered to the ECG[13,14].

The Hemopump (Medtronic Inc., Minneapolis, MI) is also used in beating heart CABG, but only to support the left ventricle during CABG of single or easily accessible vessels[15,16]. One study compared right and left heart bypass with the Biomedicus device and concluded that only right heart bypass could restore cardiac function during OPCABG[17].

It is hypothesized that (a) cardiac tilting reduces right ventricular filling which results in a decreased cardiac output and that (b) right ventricular support is thus the best way to counteract this effect. Because tilting and right ventricular support are interventions that affect both ventricles, simultaneous left and right ventricular pressure-volume loops were used to test these hypotheses.

4.3 Animals and methods

4.3.1 Animals and medication

All animals received humane care in compliance with the Guide for the Care and Use of Laboratory Animals (NIH publication 86-23, revised 1985) and the study was approved by our institution's animal ethics committee.
Seven female Texelaar sheep with an average weight of 68 kg (range 61-76 kg) were premedicated with atropine (s.c. 0.2 mg/kg). Anesthesia was induced with sodium thiopental (i.v.-bolus 15 mg/kg) and maintained with halothane (2%). After administration of muscle relaxant suxamethonium (i.v.-bolus 0.1 mg/kg) and analgetic buprenorfine (i.v.-bolus 0.01 mg/kg), a midsternotomy was performed, the pericardial sac was opened and lidocaine (i.v.-bolus 100 mg and i.v.-infusion 1 mg/kg per h) was given to prevent arrhythmia during heart manipulation. Heparin (i.v.-bolus 100 IU/kg) was administered and the activated clotting time was measured and kept above 400 s during the experiment. The animals were killed with an overdose of pentobarbital (i.v.-bolus 200 mg/kg).

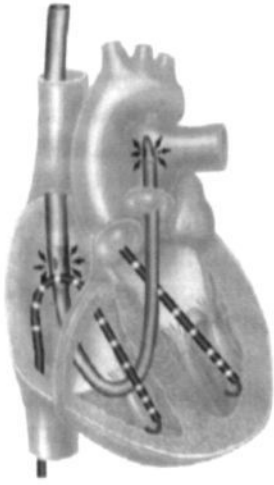

Figure 4-1: Cartoon showing the Enabler catheter positioned in the right heart. Conductance catheters are placed in both ventricles with their pigtail in the ventricular apex.

4.3.2 Instrumentation

A Doppler aortic flow probe (Transonic, Ithaca, NY) was placed on the descending aorta and compared to thermodilution-derived cardiac output to include flow to the coronary arteries and the upper body, which was assumed to be a fixed percentage for the remainder of the experiment. Two

conductance catheters (ANP-223N, Sentron, Roden, The Netherlands) were placed under fluoroscopy in the left and right ventricles via the femoral artery and jugular vein, respectively, (Figure 4-1) and connected to two Leycom Sigma-5DF systems (Cardiodynamics, Leiden, The Netherlands).

The Enabler catheter was placed via the jugular vein (right atrium in one sheep) through the right ventricle into the pulmonary artery, so that the catheter's inlet valve was positioned in the right atrium and the outlet valve was positioned in the pulmonary artery (Figure 4-1).

4.3.3 Measurements

The measurement protocol started with cardiac tilting by the Octopus device to expose the inferior wall, as described elsewhere[12]. After 5 min of unsupported tilting, the right ventricular support was activated at its maximum flow of 1.6 l/min for 10 min. In one sheep a posterior wall tilting procedure was performed[12]. The recorded hemodynamic signals included ECG, right and left ventricular pressure and volume, cardiac output and pump flow settings. Measurements were done at baseline, 5 min of cardiac tilting and 10 min of right ventricular support.

4.3.4 Conductance calibration

Parallel conductance was determined by the method described elsewhere[5]. Absolute volumes were determined by comparing conductance-derived stroke volume with the stroke volume measured by the aortic flow probe. Because the aortic flow probe measures the sum of both right ventricular support and right ventricular output, the right ventricular slope factor during activation of the right ventricular support was assumed to be the average of the slope factor before and after the activation.

4.3.5 Data analysis

All conductance measurements were analyzed with the Circlab 99 software package (Paul Steendijk, Leiden, The Netherlands). A non-parametric Friedman test with α=0.01 was used to select those variables in which at least one stage (baseline, tilt or right ventricular support) was different from the other stages. In these selected variables, statistically significant differences between the baseline, tilted and right ventricular support stages were tested using a paired t-test with Bonferroni correction for three multiple measures. Significance was assumed if the corrected P value was less than 0.05.

4.4 Results

4.4.1 Cardiac tilting

In Table 4-1, hemodynamic data from the conductance measurements are summarized. They show that tilting caused a strong and significant reduction in cardiac output of 31%. This reduction was accompanied by a decrease in right ventricular end-diastolic volume of 44%, while end-diastolic pressure rose slightly but not significantly. These effects are also seen in the examples of pressure-volume loops given in Figure 4-2. Left ventricular pressure did not significantly decrease and even increased in two animals upon tilting.

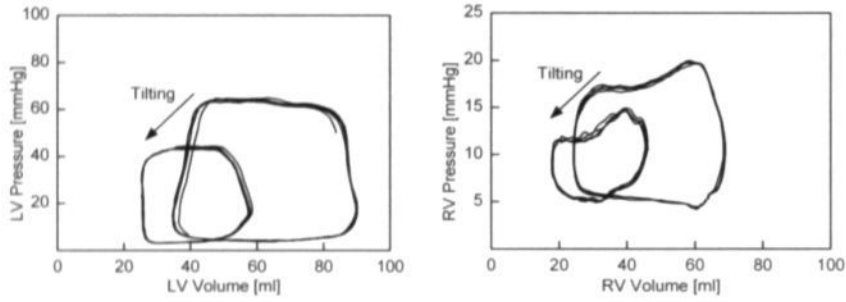

Figure 4-2: Representative left and right ventricular pressure-volume loops before and after tilting with the Octopus device. Upon tilting the stroke volume, left ventricular end-systolic pressure and right ventricular end-diastolic volume decrease, but right ventricular end-diastolic pressure increases.

The ventricles reacted differently to cardiac tilting. This was best seen at the end of the tilting procedure; when the heart was placed back into its normal position, it was observed that the right ventricle immediately responded to the new situation while it took a number of beats for the left ventricle to adjust (Figure 4-3).

4.4.2 Right ventricular support

The Enabler right ventricular support system mildly increased cardiac output and left ventricular end-diastolic volume, but not significantly, and cardiac output remained 23% lower than the pre-tilting value (Table 4-1). Upon right ventricular support activation, the right ventricular output was decreased by more than 0.5 l/min in five out of seven experiments.

These effects are seen in the examples of pressure-volume loops given in Figure 4-4 and a similar result was obtained with the right ventricular support in the untilted heart as shown in Figure 4-5; right ventricular stroke volume was strongly decreased when the right ventricular support was switched on, while left ventricular stroke volume only mildly increased.

Table 4-1: Hemodynamic changes with tilting and subsequent right ventricular support

	Baseline	Tilting	RV support
Overall function			
HR (bpm)	126 ± 19	133 ± 17	128 ± 20
CO† (l/min)	4.4 ± 0.9	3.1 ± 0.9*	3.4 ± 0.6*
RVO† (l/min)	4.4 ± 0.9	3.1 ± 0.9*	2.4 ± 0.5*
LVESP (mmHg)	58 ± 12	44 ± 10	47 ± 6.9
RVESP (mmHg)	18 ± 2.5	19 ± 3.0	18 ± 3.7
Left ventricle			
EDV (ml)	93 ± 24	72 ± 30	76 ± 22
ESV (ml)	54 ± 27	48 ± 33	49 ± 26
EDP (mmHg)	8.3 ± 2.2	9.0 ± 2.2	8.7 ± 1.4
Right ventricle			
EDV† (ml)	86 ± 41	51 ± 35*	50 ± 31*
ESV† (ml)	50 ± 34	28 ± 27*	30 ± 26*
EDP (mmHg)	5.6 ± 3.5	6.9 ± 4.2	6.4 ± 4.4

HR, heart rate; CO, cardiac output; RVO, right ventricular output; LVESP, left ventricular end-systolic pressure; RVESP, right ventricular end-systolic pressure; EDV, end-diastolic volume; ESV, end-systolic volume; EDP, end-diastolic pressure. All data are the mean±SD and n=7 (except left ventricular EDP, n=6). †One stage different using the Friedman test with α=0.01 (see Methods Section). *P<0.05 versus baseline. None of the variables measured during right ventricular support were significantly different from the tilted position.

4.5 Discussion

The results of this study demonstrate that simultaneous left and right ventricular pressure-volume loops measured by conductance catheters are useful to examine changes in cardiac function during cardiac tilting and subsequent right ventricular support by the Enabler. The conductance technique has been used successfully earlier in the assisted heart[3,4], but the heart was never placed in a non-anatomical position and both ventricles were never simultaneously studied during or after an intervention. This study not only shows that this is feasible, but also that it is necessary in a complicated intervention in order to know which ventricle causes a change in cardiac function, and which ventricle merely responds to the other.

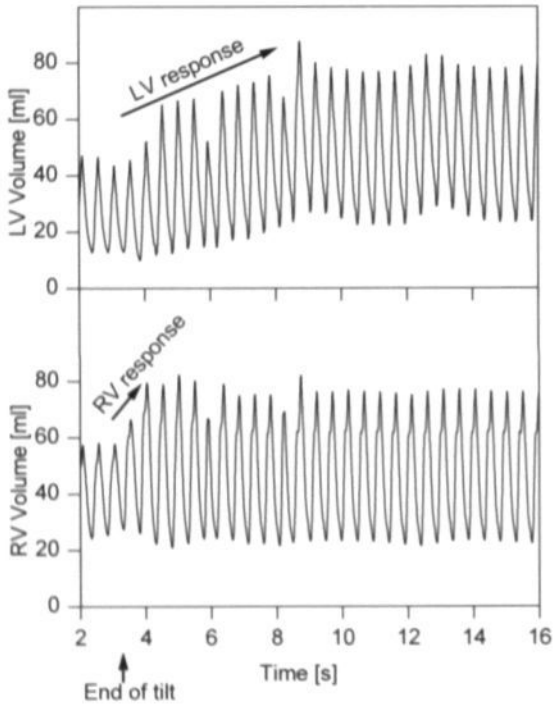

Figure 4-3: Changes in left and right ventricular volume upon repositioning of the heart from a tilt into its normal position. The repositioning occurs between t=3 s and t=4 s. The slow variation in volume, especially seen in the left ventricle, is caused by ventilation. The right ventricle immediately responds to the new situation by an increase in end-diastolic volume within two to three beats. In contrast, the left ventricle slowly accommodates to the new situation in about ten beats.

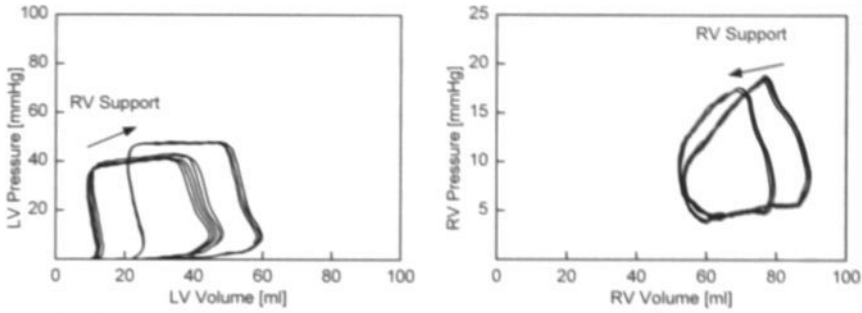

Figure 4-4: Representative left and right ventricular pressure-volume loops before and after Enabler right ventricular support with the Enabler in the tilted heart. The left ventricular stroke volume and end-systolic pressure are increased upon right ventricular support. In contrast, the right ventricular stroke volume is decreased when the right ventricular support is switched on; the difference in stroke volume between left and right ventricles is caused by the right ventricular support.

4.5.1 The effect of tilting on cardiac function

Cardiac tilting causes a strong decrease in cardiac output. In the present study, this decrease was on average 31%, which is somewhat less than found by others in healthy pigs[9,10,17] and sheep[14]. Interestingly, cardiac output was much more decreased than left ventricular systolic pressure, as was observed previously[14]. Even more importantly, left ventricular systolic pressure was increased upon tilting in two out of seven sheep. This shows that blood pressure alone is most likely not a sensitive measure to estimate the extent of the hemodynamic worsening during cardiac tilting in the individual patient.

The observed decrease in cardiac output can be caused by (a) an increase in afterload, (b) a valvular defect, (c) a decrease in contractility or (d) a decrease in preload in either ventricle.

a) Afterload is not increased during cardiac tilting, as the end-systolic pressure in both left and right ventricles does not increase. Therefore, kinking of the aorta or the pulmonary artery does not seem to occur.
b) The introduction of a valvular defect by tilting was discarded earlier by echocardiography observations in two previous studies[9,17].

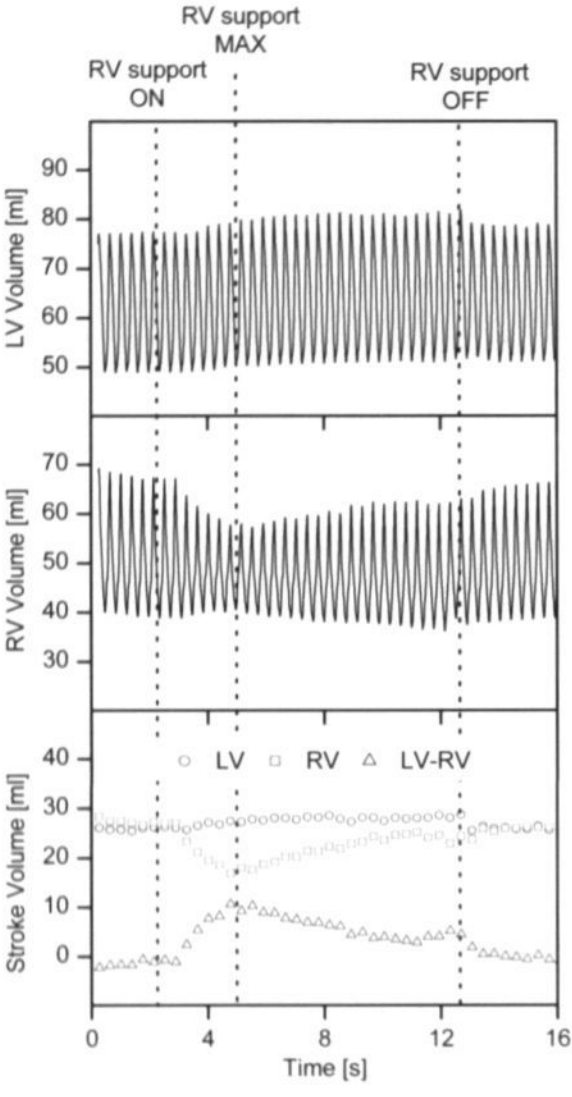

Figure 4-5: Enabler right ventricular support with the heart in its anatomical position. The Enabler is switched on at t=3 s up to maximum flow (2.0 l/min) at t=5 s and then slowly turned back to zero flow at t=13 s. The left ventricular stroke volume and end-diastolic volume are slightly increased upon right ventricular support. The right ventricular stroke volume and end-diastolic volume decrease strongly when the Enabler is switched on. This unloading limits the Enabler's positive effect on left ventricular stroke volume.

c) An acute decrease in contractility upon tilting is unlikely. No signs of tilting-induced ischemia were reported by other investigators[10] and hypoxia, which may occur due to low blood pressure during tilting, is more likely a consequence than a cause of the low cardiac output. One of the most reliable measures of contractility is the slope of the end-systolic pressure-volume relationship. Although this slope can be measured with a conductance catheter, this was not done as it requires caval vein occlusion, which would have interfered too much with the hemodynamic state of these animals during tilting.
d) A decrease in preload, defined as end-diastolic volume, occurs in both ventricles upon tilting. The right ventricle can be argued to be the most likely cause of the decrease in cardiac output for two reasons. First, the right ventricle immediately reacts to the end of the tilt by increasing its end-diastolic volume and stroke volume, while the left ventricle slowly reacts to the increased filling by the Frank-Starling mechanism (Figure 4-3). If the left ventricle was the problem during tilting, then it would have been the first to react to the end of the tilt. Second, a resistance to left ventricular filling would have increased pulmonary pressure and thus right ventricular afterload, which was not observed. In conclusion, reduced right ventricular filling is the major cause of the decrease in cardiac output during cardiac tilting.

The reduced right ventricular filling is not accompanied by a decrease in right ventricular end-diastolic pressure. This contradiction was observed before[9,10,17], and may be caused by a mechanical inhibition of right ventricular filling, for instance a compression of the ventricular wall by the tilting procedure. This is supported by a recent echocardiographic study which reported that right ventricular geometry changes during tilting[17]. Another explanation is that the ventricle is filled against gravitation because the apex is pointed upwards during tilting.

It has been shown that an extreme 20° Trendelenburg maneuver can partially restore cardiac function during a tilt via increased right heart filling pressure and thus increased preload[9,10]. This is in agreement with our finding that right ventricular filling is the problem during cardiac tilting. However, it should be noted that the reported acute two-fold increase in right atrial pressure caused by the Trendelenburg maneuver has the inherent risk of atrial fibrillation[18], and should therefore be avoided if possible.

4.5.2 Right ventricular support with the Enabler

The Enabler right ventricular support is not able to fully recover cardiac output to pre-tilting values. Our results correspond well with the recently published results with the Biomedicus device and the Enabler as a right

heart bypass, which were also shown to only partially restore cardiac function[14,17]. Another support system, the Hemopump, has also been used in OPCABG[15,16], but this is a left ventricular assist device and might not be suitable, as it is the right ventricle that needs support.

There are two explanations why the Enabler did not fully restore cardiac output. First, activation of the Enabler further decreases right ventricular output. Likely mechanisms are a reduction in right ventricular filling because the Enabler sucks blood from the right atrium, or an increase in right ventricular afterload caused by simultaneous ejection of the Enabler and the right ventricle. Second, the forward flow of the Enabler, the difference between right and left ventricular output (see Table 4-1), is only 0.9 l/min. Possible explanations are (a) the right ventricular output is overestimated because the conductance slope factor can not be measured (see Methods Section), and (b) the Enabler causes regurgitation across the pulmonary valve, which would mean that part of the Enabler output is used to fill the right ventricle rather than flowing towards the lungs.

In conclusion, current right ventricular support systems can not fully restore cardiac function during tilting. Furthermore, the output of a right ventricular support should not be assumed to be a net extra output, and monitoring of the end result, cardiac output, is therefore crucial.

4.5.3 Limitations of the study

In this study, the animals had low blood pressure, cardiac output, ventricular volumes and poor ventricles compared to humans. It can be expected that tilting will be better tolerated by the human heart.

4.6 Acknowledgements

This study was financially supported by Hemodynamics Systems Ltd., Yoqneam, Israel. We gratefully acknowledge the biotechnical assistance provided by Jo Habets and Theo van der Nagel, the study support by Veronica Elias-Weissmann, and the comments on the manuscript by David Shoshani.

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Chapter 5

Right ventricular support

Published as:

Geskes GG, Dekker AL, van der Veen FH, Cramers AA, Maessen JG, Shoshani D, Prenger KB. The Enabler right ventricular circulatory support system for beating heart coronary artery bypass grafting. Ann Thorac Surg 1999;68:1558-1561.

5.1 Abstract

Background

Beating heart coronary artery bypass graft surgery of the left anterior descending, diagonal, and right coronary artery can be performed safely with the Octopus Stabilization System. However, tilting of the heart, which is necessary to reach the obtuse marginal and distal right coronary arteries, causes hemodynamic instability. This study was performed to investigate the possible role of the Enabler right ventricular circulatory support system in counteracting this instability.

Methods

In 8 sheep, the Enabler cannula was introduced via the jugular vein and positioned with the inlet valve in the right atrium and outlet valve in the pulmonary artery. The Octopus was used to expose the inferior wall and the posterior wall of the left ventricle. The hemodynamic effects of this tilting with and without Enabler right ventricular support were recorded, including Pressure Volume (PV) loops measured by conductance catheters in both ventricles.

Results

Tilting caused a reduction in stroke volume (inferior 31%, posterior 17%) and Enabler activation increased stroke volume (inferior 13%, posterior 31%).

Conclusion

Tilting the heart has severe hemodynamic consequences that can be partially counteracted by the use of the Enabler for right ventricle support.

5.2 Introduction

It has been demonstrated that beating heart revascularization of the coronary arteries on the anterior and inferior walls of the heart can be performed safely with excellent results. This advancement is due to the introduction of stabilizers such as the Octopus Tissue Stabilization System (Medtronic, Grand Rapids, MI), which stabilize the left anterior descending (LAD), diagonal, and the right coronary arteries. The Octopus also allows access to the obtuse marginal and distal right coronary arteries. However, performing beating heart coronary artery bypass graft surgery (CABG) to these vessels is limited by hemodynamic instability that results from tilting the heart to reach the posterior and inferior wall of the left ventricle[1].

Tilting leads to a dysfunction of the left and/or right ventricle and causes a decrease in cardiac output and systemic blood pressure. One way to maintain an acceptable cardiac output is the use of the Trendelenburg maneuver to increase the right-sided filling pressures and thereby partially correct the low output of the left ventricle[2].

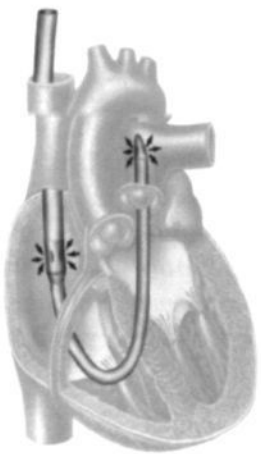

Figure 5-1: The position of the Enabler cannula. The inflow valve lies centrally within the right atrium, the outflow tip lies proximally in the pulmonary artery.

However, the safety of this method in case of a heart with an abnormal ejection fraction of the left and/or right ventricle has not yet been proven.

It is widely understood that heart tilting leads to a dysfunction of the left and right ventricle and causes a decrease in cardiac output and systemic blood pressure. However, it is unclear whether the ventricular problems are interdependent, and if so, which ventricle is the source of the problem.

The purpose of this sheep study was to evaluate the effectiveness of a new right-side support system (Enabler circulatory support system; Hemo-Dynamics, Yokneam, Israel)[3] in overcoming both right and left ventricular compromise during tilting. In addition, the impact of the device on tissue damage and hemolysis was examined.

5.3 Materials and methods

5.3.1 Animals and medication

Eight healthy female sheep of average weight 66 kg were used in this study. The animals were premedicated with atropin (10 mg), and anesthesia was induced with thiopental (15 mg/kg, iv). After endotracheal intubation, anesthesia was maintained with oxygen/nitrous oxide (2:1) and halothane (1% to 2%). At the end of the experiment, the sheep were killed with pentobarbital (Euthesate, 200 mg/kg, iv) and KCl. Before introduction of the Enabler cannula, heparin was administered (300 IU/kg bodyweight as a bolus). During the procedure, the ACT was maintained at more than 400 s.

5.3.2 Description of the Enabler system

The Enabler circulatory support system consists of a control console, a disposable pump-head, and a cannula. The control console is connected by means of a tube to the lower chamber of the pump-head. This tube is filled with water. The pump-head contains two chambers that are separated by a flexible diaphragm. The cannula is connected to the pump-head's upper chamber and is filled with a sterile isotonic solution that mixes with the patient's blood upon introduction. The electro-hydraulic control console is 1:1 triggered by the patient's electrocardiogram and activates a servo-controller that manages the cyclical movement of water between the control console and the pump-head. As water is pushed into and out of the pump-head, the diaphragm moves accordingly, thereby driving the blood in the catheter. The cannula sits in the right heart, with an inlet port in the right atrium and the outlet tip in the pulmonary artery. A series of valves within the cannula causes blood to be sucked through the inlet port and expelled through the outlet tip during activation of the control console and pump-head.

5.3.3 Experimental protocol

After sternotomy, the 24 French Enabler cannula was introduced via the jugular vein and advanced through the right atrium, tricuspid valve, right ventricle, and pulmonary valve. The distal tip of the cannula was positioned in the proximal pulmonary artery, and the inlet port in the right atrium (Figure 5-1). The Octopus stabilizer was then used to tilt the heart in such a way that the distal branches of the right coronary artery were exposed. After 5 minutes of unsupported tilting, the Enabler was activated during 10 minutes with a pulsatile flow of 2.0 L/min. The Enabler was then deactivated for 2 minutes, after which the heart was placed back in its normal position.

After a 30-minute resting period, a second tilting procedure was performed to expose the posterior wall of the left ventricle with the distal obtuse marginal branches. Again, the procedure entailed 5 minutes of unsupported tilting, 10 minutes of Enabler supported tilting, and 2 minutes of unsupported tilting, after which the heart was placed back in its original position. At the end of this procedure, the animals were killed and the right atrium, right ventricle, and pulmonary artery were inspected macroscopically for signs of damage to the endocardium and valves.

5.3.4 Hemodynamic recordings

Hemodynamic recordings, including left and right ventricular pressure-volume loops, were obtained with a Swan-Ganz catheter (Arrow, Reading, PA) inserted via the jugular vein, a femoral arterial, and direct left atrial pressure line (Baxter, Santa Ana, CA), a left ventricular conductance catheter inserted via the femoral artery, a right ventricular conductance catheter inserted via the jugular vein (Sentron, Roden, The Netherlands), and a Doppler flow probe (Transonic, Ithaca, NY) on the descending aorta for continuous cardiac output measurement. To obtain absolute cardiac output values with the flow probe, including coronary and carotid artery flow, the Doppler flow probe was calibrated in situ against the cardiac output measured with the Swan-Ganz catheter by the thermodilution method. Left and right ventricular pressure-volume loops were captured via the conductance catheters with two Leycom Sigma 5 conductance consoles (Cardiodynamics, Leiden, The Netherlands)[4,5]. Absolute volume measurements were obtained by calibration of the conductance signals to the cardiac output as measured by the flow probe, and saline injections were used to estimate the parallel conductance according to the method introduced by Baan and associates[6]. Tilting the heart changes the position of the conductance catheter in the ventricle and makes any previous calibration invalid, so each time the ventricle was tilted or placed back in its anatomical position, a full calibration procedure was performed.

Hemodynamic data were obtained with: (1) the heart in its normal position, (2) with the heart tilted but without support of the Enabler, and (3) with the heart tilted and supported by the Enabler. In the statistical analysis, absolute and percentage changes between these three situations were analyzed using a Student's t test, with significance assumed if the p value was less than 0.05.

5.3.5 Hemolysis

Whether the Enabler pumping induces hemolysis was assessed by measuring free hemoglobin in blood plasma samples. Venous blood samples were obtained before insertion of the Enabler catheter, immediately

after the inferior wall tilting procedure, and after the posterior wall tilting procedure. Free hemoglobin was measured at 540 and at 575 nm, and values were averaged to obtain the percentage of hemolyzed erythrocytes in the blood, which can be used to calculate the free hemoglobin in milligrams per liter. This measurement is assumed to be more accurate at low free hemoglobin values than measuring free hemoglobin directly in milligrams per liter[7].

5.4 Results

For several reasons, the protocol could not be completed fully in all 8 animals. In sheep no. 2, the Enabler cannula dislocated from the pulmonary artery during tilting and could therefore not give any circulatory support. Sheep no. 5 developed ventricular fibrillation during posterior wall tilting due to hypoxia caused by ventilator malfunction. In sheep no. 7, posterior wall tilting caused severe myocardial ischemia, so the protocol had to be abandoned. As a consequence, sheep no. 2 was excluded from all analysis, and the hemodynamic data from the posterior wall tilting in sheep nos. 5 and 7 were also excluded from the analysis.

5.4.1 Hemodynamic recordings

The hemodynamic data presented in Table 5-1 and Table 5-2 show that tilting for the exposure of the inferior wall caused a significant decrease compared with baseline values in stroke volume (31% ± 9%), cardiac output, and right ventricular volumes, and a significant increase in right atrial pressure. Activating the Enabler significantly increased stroke volume (13% ± 8%) and left ventricular volumes compared with the volumes during unsupported tilting. The posterior wall hemodynamic data in Table 5-1 and Table 5-2 show the same general results with an average decrease (compared with baseline) in stroke volume of 17% ± 7% due to tilting and an increase (compared with unsupported tilting) of 38% ± 15% with activation of the Enabler. However, due to the limited number of sheep, significance for posterior wall tilting could not be confirmed.

5.4.2 Pressure-volume loops

A representative example of the effect of tilting and Enabler pumping on the pressure-volume loops of both ventricles is presented in Figure 5-2. The tilting procedure reduced stroke volume in both ventricles, while switching on the Enabler increased left ventricular performance while further decreasing right ventricular pumping function.

5.4.3 Hemolysis

Before insertion of the catheter, the average amount of free hemoglobin was 255 ± 65 mg/L (n = 6), and this increased to 390 ± 65 mg/L (n = 6) after the inferior wall tilting/pumping procedure. After the second, posterior wall tilting/ pumping procedure amount of free hemoglobin was 422 ± 162 mg/L (n = 6).

5.4.4 Macroscopic examination

Upon macroscopic examination, no damage was found to the right atrium, right ventricle, and pulmonary artery.

Table 5-1: Hemodynamic measurements (left-sided) during tilting.

Parameter	Situation	Inferior Tilt	Posterior Tilt
CO (l/min)	Normal	4.3 ± 1.2	3.6 ± 1.6
	Tilted	3.1 ± 0.9*	3.0 ± 1.0
	Enabler On	3.3 ± 0.8	3.8 ± 1.0**
LAP (mmHg)	Normal	5.9 ± 0.6	6.0 ± 1.6
	Tilted	6.6 ± 1.1	7.7 ± 0.8*
	Enabler On	6.6 ± 1.6	9.1 ± 1.9
LVESP (mmHg)	Normal	62 ± 14	47 ± 13
	Tilted	51 ± 12	42 ± 12
	Enabler On	53 ± 9	53 ± 12**
LVESV (ml)	Normal	41 ± 28	74 ± 36
	Tilted	44 ± 15	51 ± 30
	Enabler On	50 ± 13**	65 ± 40
LVEDV (ml)	Normal	79 ± 21	110 ± 30
	Tilted	67 ± 14	80 ± 37
	Enabler On	75 ± 13	99 ± 45

CO = Cardiac Output; LAP = Left Atrial Pressure; LVEDV = Left Ventricular End Diastolic Volume; LVESP = Left Ventricular End Systolic Pressure; LVESV = Left Ventricular End Systolic Volume
* $p<0.05$ tilted vs. normal; ** $p<0.05$ Enabler on vs. titled.

Table 5-2: Hemodynamic measurements (right-sided) during tilting

Parameter	Situation	Inferior Tilt	Posterior Tilt
RAP (mmHg)	Normal	9 ± 2	11 ± 3
	Tilted	11 ± 2*	12 ± 2
	Enabler On	--	--
RVESP (mmHg)	Normal	20 ± 2	20 ± 1
	Tilted	20 ± 3	20 ± 1
	Enabler On	19 ± 3	21 ± 2
RVESV (mmHg)	Normal	42 ± 24	51 ± 25
	Tilted	26 ± 21*	33 ± 10
	Enabler On	27 ± 21	34 ± 11
RVEDV (ml)	Normal	71 ± 28	79 ± 36
	Tilted	45 ± 26*	58 ± 16
	Enabler On	44 ± 24	54 ± 16

RAP = Right Atrial Pressure; RVEDV = Right Ventricular End Diastolic Volume; RVESP = Right Ventricular End Systolic Pressure; RVESV = Right Ventricular End Systolic Volume
* $p<0.05$ tilted vs. normal; ** $p<0.05$ Enabler on vs. titled.

5.5 Discussion

The results of this experimental study in sheep show that tilting of the heart to reach the obtuse marginal branches on the posterior wall of the left ventricle and the distal branches of the right coronary artery on the inferior wall causes a significant impairment of right ventricular function and a reduction of left ventricular output. It is not clear whether this impairment of right ventricle function is the result of inflow obstruction of the blood by traction on the inferior caval vein, or the result of disturbance of the contractions of the right ventricle, or the development of tricuspid regurgitation[3]. The decrease in left ventricular output could be caused by right ventricular dysfunction but also by valve regurgitation or a decrease in myocardial contractility. In any event, the Enabler bypasses all of these potential sources of the problem, thus partially compensating the decreased right ventricular function by serving as a right heart support system. By increasing the cardiac output on the right side of the heart, the output of the left ventricle increases as well.

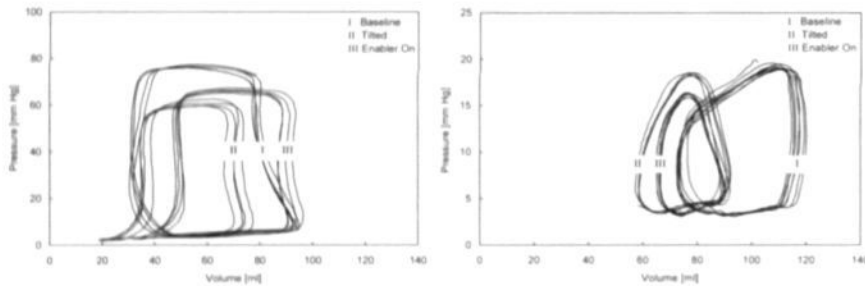

Figure 5-2: Typical pressure-volume loops obtained with a conductance catheter (sheep no.6). Left: Left ventricle. Baseline stroke volume 45ml; Tilted stroke volume 34ml; Enabler On stroke volume 40ml. Right: Right ventricle. Baseline stroke volume 43ml; Tilted stroke volume 33ml; Enabler On stroke volume 23ml. Enabler set at 2.0 L/min (Enabler stroke volume 17ml).

There was an increase in free hemoglobin observed after pumping. It is not clear whether this is induced by the pump itself or by the tissue trauma caused by the surgical procedure. A full safety study of the Enabler circulatory support system is currently being conducted, during which we will try to establish the cause of this increase in free hemoglobin.

Our results confirm that the Enabler circulatory support system is able to pump blood from the right atrium into the pulmonary artery, and as such, can function as a right ventricular support system. We have found no signs of damage to the endocardium or the tricuspid and pulmonary valve, and minor hemolysis.

The current model of the Enabler, which provides a flow of 2 to 2.5 L/min, gave partial support to the right ventricle in this study. However, the net extra cardiac output due to the Enabler was only 0.3 L/min during the inferior wall tilt and 0.8 L/min during the posterior wall tilt. The difference between provided flow, and net extra cardiac output was caused by a decrease in right ventricular output during the activation of the Enabler. In effect, the Enabler bypasses the right ventricle, creating either a decrease in preload or an increase in afterload, which ultimately results in a reduction of right ventricular output.

Introduction of the cannula via the jugular vein in humans will not be possible due to the cannula's 24 French size. Instead, introduction via the right atrium or right auricle should be used in human sternotomy cases. Another possible application of the femoral version of the Enabler is as a temporary right heart assist device in a patient with a failing right ventricle after cardiac surgery or a myocardial infarction of the right ventricle.

A limitation of this study was that all animals had low cardiac output and filling pressures before starting the protocol.

The Enabler gives partial support to the right ventricle during cardiac tilting necessary to reach the posterior and inferior wall of the left ventricle without causing tissue damage or significant hemolysis. Further study is necessary to isolate the nature of the right and left ventricle problem during cardiac tilting.

5.6 Acknowledgements

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Chapter 6

Intra Aortic Balloon Pump in acute mitral regurgitation

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6.1 Abstract

Objectives
Acute mitral regurgitation (MR) is present in 10% of patients presenting with cardiogenic shock. To stabilize these patients intra-aortic balloon pumping (IABP) is recommended, but the mechanism of IABP support in these patients is unknown. This animal study was designed to describe the hemodynamic effect of intra-aortic balloon pumping during cardiogenic shock induced by acute mitral regurgitation.

Methods
In eight calves, left ventricular pressure-volume loops, aortic and left atrial pressure and aortic, carotid artery and coronary blood flow were recorded. Acute mitral regurgitation (MR) (range 36-79%) was created by placing a metal cage in the mitral valve. Hemodynamic data was obtained at control, during acute MR and during acute MR with 1:1 IABP support.

Results
Acute MR caused a decrease in cardiac output (-32%, p=0.018), blood pressure and carotid artery flow while left ventricular output (+127%, p=0.018), end-diastolic volume and left atrial pressure all significantly increased. Stroke work, ejection fraction and coronary blood flow were not significantly changed and no signs of ischemia were seen on the ECG.
The IABP raised average cardiac output by 31% (p=0.012) and significantly raised blood pressure and flow to the brains while decreasing systemic vascular resistance. Left ventricular function and mean coronary blood flow did not change, but diastolic coronary flow became more important as shown by the increase in diastolic fraction from 64 to 95 %. (p=0.028). Average mitral regurgitation dropped by 7.5 % (p=0.025).

Conclusion
In conclusion, application of the IABP during acute MR, lowers aortic impedance resulting in less mitral regurgitation and more output towards the aorta without changing left ventricular function.

6.2 Introduction

Acute mitral regurgitation (MR) is present in 10% of the patients presenting with cardiogenic shock[1]. Acute MR is the result of papillary muscle rupture caused by endocarditis, degenerative disease of the mitral valve or myocardial infarction. The actual size of the infarction is often quite limited which illustrates that acute MR may induce cardiogenic shock[2-4]. Definite treatment is surgical repair of the mitral valve but immediate hemodynamic support should be instituted to stabilize patients before they undergo surgery. During this period, cardiac output and blood pressure need to be restored using the intra-aortic balloon pump (IABP) and vasodilators such as nitroprusside[5-8].

The effect of vasodilators in acute MR models has been studied extensively[7,9], but the hemodynamic effect of the IABP during acute MR has not been documented.
The general hypothesis on the effect of the IABP in acute MR cases is that the afterload reduction by the IABP results in more output towards the aorta than to the atrium. This will reduce the severity of the mitral regurgitation and increase the cardiac output of the left ventricle. In addition, two known beneficial effects of the IABP may occur: The afterload reduction itself may cause a higher output of the left ventricle while diastolic counterpulsation could increase coronary blood flow which may be beneficial to left ventricular contractility.

In this study, these hypotheses on the hemodynamic effects of the IABP are tested in an animal model of acute mitral regurgitation.

6.3 Materials and Methods

6.3.1 Animal preparation

All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" (NIH publication 86-23, revised 1985) and the study was approved by our institution's animal ethics committee. Eight "Roodbont" calves with average weight 109kg (76-148kg) were premedicated with atropine (0.05 mg/kg s.c.). Anesthesia was induced with sodium thiopental (i.v.-bolus 15mg/kg) and maintained with a 1:2 mixture of O_2:N_2O and halothane (2%). After administration of muscle relaxant suxamethonium (i.v.-bolus 0.1 mg/kg) and analgetic buprenorfine (i.v.-bolus 0.01 mg/kg), a left thoracotomy was performed and ventilation was modified to give a peak end-expiration pressure of 5cm H_2O. Heparin (i.v.-bolus 100 IU/kg) was administered and the activated clotting time was measured and kept above 400 seconds during the experiment. During anesthesia, monitoring included ECG, blood pressure, oxygen saturation and capnography. The animals were killed with an overdose of pentobarbital (i.v.-bolus 200 mg/kg).

6.3.2 Instrumentation

Under fluoroscopy a Swan-Ganz thermodilution catheter (Arrow International, Reading, PA, USA) was advanced via the jugular vein and a 40ml intra-aortic balloon (Datascope, Fairfield, NJ, USA) was placed via the right femoral artery in the high descending aorta. A conductance catheter, incorporating a pressure sensor (Sentron, Rhoden, the Netherlands), was placed via the right carotid artery in the left ventricle. The conductance catheter was connected to a conductance console (CD Leycom, Zoetermeer, the Netherlands) which was used in dual frequency mode[10]. Solid-state pressure catheters (Sentron, Rhoden, the Netherlands) were placed in the abdominal aorta via the left femoral artery, in the ascending aorta via the left carotid artery and in the left auricle through a small incision. Flow probes (Transonic Systems, Ithaca, NY) were placed on the ascending aorta, the left carotid artery and on a side branch of the left anterior coronary descending artery. From the latter signal, the diastolic fraction was calculated to differentiate between systolic and diastolic coronary blood flow[15].

To create the acute mitral regurgitation an incision was made in the left atrium through which a retrievable steel wire cage (Günther tulip vena cava filter, William Cook Europe, Bjaeverskov, Denmark), was placed in the mitral valve (Figure 6-1). The amount of mitral regurgitation was defined as the percentage of left ventricular stroke volume flowing towards the atrium.

This percentage was calculated by the subtracting aortic flow (by flow probe) from left ventricular stroke volume (by conductance catheter) and dividing by left ventricular stroke volume.

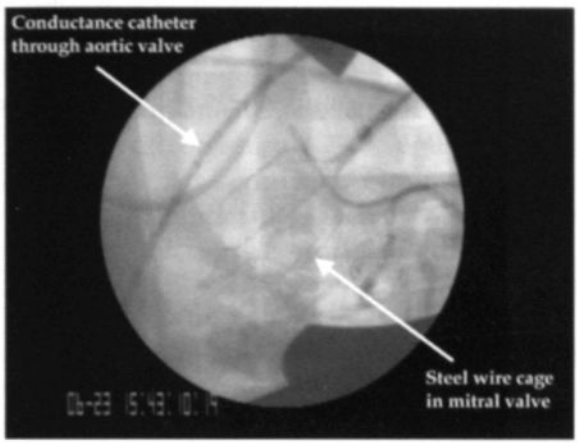


Figure 6-1: Fluoroscopic image which shows the steel wire cage in the mitral valve and the conductance catheter through the aortic valve.

6.3.3 Conductance calibration

Parallel conductance was determined by injecting 7.5 ml of 6.5% hypertonic saline in the pulmonary artery[11]. A 5 ml blood sample was collected and blood resistivity measured by a sampling cuvette (CD Leycom, Zoetermeer, the Netherlands)[12]. The slope factor was determined by comparing conductance derived stroke volume with the aortic flow just prior to the creation of acute mitral regurgitation.

6.3.4 Measurement protocol

After instrumentation, the animal was stabilized for at least thirty minutes. After this period, the control measurements were performed. Then acute MR was created by stenting the mitral valve with a steel wire cage as described above. Once the animal was hemodynamically stable, which usually took only a couple of beats, the unsupported acute MR measurement was performed. Immediately after this measurement the IABP support was switched on and, again after stabilization, measurements were performed. After these 1:1 IABP-supported measurements, the acute MR was relieved by pulling back the steel wire cage.

6.3.5 Statistical analysis

A non-parametric Friedman test was used to select those variables in which at least one stage (control, unsupported acute MR and 1:1 IABP supported acute MR) was different from other stages. In these selected variables, statistically significant changes between control and unsupported MR and between unsupported MR and 1:1 IABP supported acute MR were tested using a non-parametric, Wilcoxon signed ranks test. Significance was assumed if the P-value was less than 0.05.

6.4 Results

6.4.1 Acute MR

Hemodynamic data are presented in Table 6-1. It shows that in all animals the introduction of the cage in the mitral valve caused severe acute mitral regurgitation (average regurgitant fraction 65%, range 36-79%). This acute MR was accompanied by a significant decrease in cardiac output (-32%, p=0.018), blood pressure (-27%, p=0.018) and carotid artery flow (-26%, p=0.018) while left ventricular output, end-diastolic volume and left atrial pressure all significantly increased. Left ventricular systolic function (ejection fraction, stroke work, dP/dt_{MAX}) and coronary blood flow was unchanged and no signs of ischemia were seen on the ECG.

Afterload dropped as shown by the lower end-diastolic aortic pressure and lower maximal left ventricular pressure. However systemic vascular resistance remained the same, indicating that the afterload reduction is caused by a sudden decrease in retrograde impedance.

These observations are also visualized in the pressure-volume loops given in Figure 6-2: By creating acute mitral regurgitation, the left ventricle produces more output due to the higher preload and lower afterload. However, the higher left ventricular output can not prevent the drop in net cardiac output and blood pressure.

6.4.2 IABP during acute MR

Table 6-1 shows that switching on the IABP immediately raised average cardiac output by 31% (p=0.012) and significantly raised blood pressure and flow to the brains. Left ventricular output and contractility (dP/dt_{MAX}, stroke work, ejection fraction) did not change. Mean coronary blood flow did not change, but a significant shift from systolic to diastolic flow was observed (diastolic fraction from 64% to 95%, p=0.028).

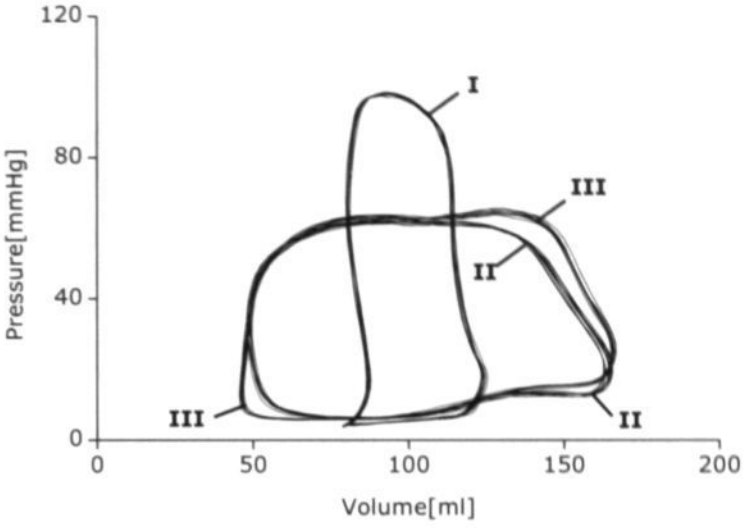
Afterload, either defined as the pressure in the ascending aorta when the aortic valve opened or as maximal left ventricular pressure, did not change significantly although systemic vascular resistance was decreased.

The above shows that left ventricular function was unchanged, while general hemodynamics improved. In the example of Figure 6-2 the same can be observed: Left ventricular pressure-volume loops did not change when switching on the IABP but blood pressure and cardiac output improved.

Table 6-1: Hemodynamic data before acute MR, during unsupported acute MR and during IABP supported acute MR.

HR	[bpm]	127	(22)	123	(25)	126	(26)
AOP_{MEAN}	[mmHg]	62.4	(11.7)	45.7	(7.7)*	51.4	(7.8)†
CO	[l min^{-1}]	2.97	(1.18)	2.03	(0.80)*	2.65	(1.17)†
LVO	[l min^{-1}]	2.96	(1.18)	6.73	(3.86)*	7.12	(3.99)
MR	[%]	0.0	(0.0)	65.4	(15.0)*	57.9	(17.5)†
Car. Flow	[l min^{-1}]	0.54	(0.22)	0.40	(0.20)*	0.48	(0.23)†
CBF	[ml min^{-1}]	59.0	(22.7)	50.6	(27.3)	49.4	(30.8)
DF	[%]	57.8	(18.4)	64.4	(21.3)	95.3	(17.5)†
Preload							
LAP	[mmHg]	8.5	(5.8)	17.1	(8.4)*	17.2	(9.3)
EDV	[ml]	65.4	(33.6)	93.1	(47.1)*	92.2	(46.8)
Afterload							
AOP_{ED}	[mmHg]	52.5	(11.3)	38.1	(6.7)*	41.8	(8.2)
LVP_{MAX}	[mmHg]	76.4	(11.4)	57.0	(8.4)*	57.5	(8.1)
SVR	[dynes s cm^{-5}]	1629	(400)	2091	(700)	1770	(622)†
Systolic function							
EF	[%]	44	(18)	62	(16)	64	(16)
dP/dt_{MAX}	[mmHg s^{-1}]	767	(167)	588	(206)	619	(215)
SW	[g m]	18.4	(12.1)	26.4	(19.4)	27.9	(21.2)

HR: Heart rate; AOP_{MEAN}: Mean ascending aortic pressure; CO: Cardiac output; LVO: Left ventricular output; MR: Mitral regurgitant fraction ([LVO-CO]/LVO); Car. Flow: Flow in the carotid artery; CBF: Coronary blood flow; DF: Diastolic Fraction; LAP: Left atrial pressure; EDV: Left ventricular end diastolic volume; AOP_{ED}: Ascending aortic pressure at end of diastole; LVP_{MAX}: Maximal left ventricular pressure; SVR: Systemic vascular resistance; EF: Ejection fraction; dP/dt_{MAX}: Maximum positive derivative of left ventricular pressure over time; SW: Stroke work performed by the left ventricle. Values are mean(sd), n=8. *$p<0.05$ vs. control; †$p<0.05$ vs. unsupported acute MR



		Control (I)	Acute MR (II)	Acute MR + IABP (III)
CO	[l/min]	4.7	3.0	4.1
LVO	[l/min]	4.7	14.6	15.1
MR	[%]	0	79	73
AOP	[mmHg]	82.5	49.7	59.8

Figure 6-2: Representative left ventricular pressure volume loops in one animal. I: Before acute mitral regurgitation, II: During unsupported acute mitral regurgitation and III: During IABP supported acute mitral regurgitation. Important hemodynamic parameters are supplied in the adjacent table. (CO: Cardiac output, LVO: Left ventricular output; MR: Regurgitant fraction; AOP: Mean ascending aortic pressure)

6.5 Discussion

6.5.1 Acute MR model and cardiogenic shock

In the clinical setting, acute MR can cause hemodynamic dysfunction resulting in cardiogenic shock and pulmonary edema[2]. In this study, acute MR was induced by placing a steel wire cage in the mitral valve. Immediately, the left ventricle increased its output but still blood pressure and net cardiac output fell by more than 25% as did carotid artery flow while left atrial pressure doubled. This combination of low cardiac output, low blood pressure, hypoperfusion with adequate intravascular volume and high left atrial pressure is indicative of cardiogenic shock[1,5].

In the present study, the animals were able to increase their average total left ventricular output (antegrade and retrograde) by +127% (p=0.018). This increase was possible due to higher filling and reduced afterload, the latter ensuring that only a limited and non-significant increase in stroke work (+43%, p=NS) was necessary to produce the extra stroke volume. This shift from pressure to volume work was purely caused by the decrease in retrograde impedance as systemic vascular resistance remained constant.

Coronary blood flow was not reduced and, as the perfusion pressure was lower, this implies coronary vasodilatation representing immediate compensation. The ECG showed no signs of ischemia, so coronary blood flow was still sufficient for the left ventricle to produce the volume work, which is energetically less costly than pressure work[13].

In accordance with other investigators[2-4], we conclude from the present study that cardiogenic shock can be caused by severe mitral regurgitation alone without any dysfunction or ischemia of the left ventricle or changes in the systemic vascular bed.

6.5.2 Effect of the IABP in acute MR

The main object of this study was to measure the hemodynamic effect of the intra-aortic balloon pump during acute mitral regurgitation. Clearly, the IABP had a beneficial effect on cardiac output and blood pressure as well as other vital parameters such as carotid artery flow. However, the cause of these effects is not immediately clear. We hypothesized the following: The IABP increases coronary blood flow resulting in higher left ventricular contractility and the IABP reduces afterload which results in more left ventricular output and/or less mitral regurgitation.

6.5.3 Effect of IABP on coronary flow and left ventricular contractility

In this study, the IABP did not increase mean coronary blood flow. A possible reason is that during acute MR, the existent coronary blood flow was already sufficient, which is supported by the absence of ischemic signs on the ECG without IABP support.
Furthermore, the IABP does not change left ventricular contractility as stroke work, $dPdt_{max}$ and ejection fraction are similar with or without support. In conclusion, the hypothesis that the IABP increases coronary blood flow resulting in higher left ventricular contractility is not confirmed by this study.

Although mean coronary blood flow was similar, the IABP did change the flow pattern: Flow during diastole increased while systolic flow decreased which led to the observed increased diastolic fraction (Table 6-1). This shift from systole to diastole was observed before in non-stenotic coronary arteries[14]. The increase in diastolic flow is caused by the IABP's counterpulsation, while the reduction in systolic flow may have three explanations:
First, there may be a reduced oxygen demand due to the unloading by the IABP which would induce metabolic vasoconstriction[14]. However, in this study the heart was not unloaded by the IABP as stroke work did not change (Table 6-1).
Second, the reduced systolic pressure by the IABP may induce or increase systolic retrograde flow[14]. However, in this study the IABP did not lower left ventricular systolic pressure (Table 6-1).
So the only explanation that agrees with our results, is that the increase in diastolic flow leads to a better myocardial perfusion[15] which induces metabolic vasoconstriction.

6.5.4 Effect of IABP on left ventricular afterload and mitral regurgitation

The observed increase in antegrade cardiac output with IABP support can be the result of lower afterload which would increase left ventricular stroke volume or because of a redistribution of antegrade versus retrograde output.

First, afterload, in its most basic definition, is the wall stress experienced by the ventricle during systole, which is calculated by systolic pressure ($\sim LVP_{MAX}$) times radius (~EDV) divided by the wall thickness. None of these parameters changed when switching on the IABP, so afterload did not change.

Second, in the normal heart, afterload is determined by the impedance of the systemic vasculature and therefore systolic wall stress and the

impedance of the systemic vasculature are closely related and used side-by-side[16]. However, in acute MR left ventricular afterload is determined by the net impedance of two parallel impedances: The aortic impedance and the retrograde impedance of the regurgitation. In our experiments, the latter was lower as is it received 65% of the flow (Table 6-1), and therefore retrograde impedance was a more important determinant of left ventricular afterload than aortic impedance.
As a result, a decrease in aortic impedance will not change afterload significantly, but will reduce mitral regurgitation and thus increase net cardiac output: A redistribution of antegrade versus retrograde output. In this study, this reduction of mitral regurgitation (-7.5 %, p=0.025) was observed when the IABP was switched on. The reduction of mitral regurgitation or retrograde output may seem small but as total left ventricular output (retrograde and antegrade) was high, it resulted in 31% (p=0.012) more antegrade cardiac output.

It is clear from the above that the only explanation for the increase in cardiac output is that aortic impedance is reduced by the IABP. This was noticed by other investigators that showed a decrease in systemic vascular resistance and in characteristic impedance[17]. This decrease in systemic vascular resistance is also seen in this study, although the appropriateness of impedance considerations is questionable as this concept is based on a time invariant impedance which is not the case if a balloon actively pumps in the aorta[18,19].

Another important consideration is the fact that, in these young animals with elastic aortas, wave velocity is limited to about 3 m s^{-1} in the aorta[20,21]. As the distance from the middle of the balloon to the aortic valve is approximately 30cm in these calves, it takes 100ms for the decrease in pressure caused by the balloon pump, to fully reach the aortic valve. As these young animals all have a high heart rate, this is not trivial: If the balloon deflates at end-diastole the full decrease in afterload reaches the aortic valve well during systole. In this respect one should also realize that the IABP is commonly triggered to give maximal afterload reduction at the tip of the balloon, where the pressure is measured.

This study shows that the IABP has a different hemodynamic effect than vasodilators in animal models of acute MR[7,9]. Vasodilators either reduce end-diastolic volume and the regurgitant orifice, or reduce afterload[7,9]. Also, vasodilators do not seem to have an optimal effect on the circulation during acute MR as they do not increase cardiac output and reduce blood pressure in these models[7,9]. In contrast, the present study shows that the IABP can raise both cardiac output and blood pressure.

6.5.5 Clinical implications

This study shows the possible benefit and mechanism of IABP support in patients with cardiogenic shock (mainly) caused by acute mitral regurgitation[1]. Others investigators have suggested that the IABP is underutilized in patients presenting with cardiogenic shock[22]. Hopefully, this study contributes to the wider use of the IABP and to clinical investigations into the effectiveness of the IABP in this special category of cardiogenic shock patients.

6.5.6 Study limitations

In this animal study we created acute MR in healthy hearts which were able to increase their left ventricular output to compensate some of the regurgitation. In the clinical situation, particularly in a patient with a myocardial infarction and coronary artery disease, the situation is more complicated and other factors could play a role, for example an increase in coronary blood flow during IABP support.
Also, patients with acute MR generally have an increased heart rate[23], which was not observed in this study as these young calves already had a high heart rate. As mentioned above, the high heart rate also masks the reduction in aortic pressure by the balloon pump.

6.5.7 Conclusion

The aim of this study was to evaluate the hemodynamic effect of the IABP during acute MR. We conclude that the IABP lowers aortic impedance resulting in less mitral regurgitation and more output towards the aorta without changing left ventricular function.

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Chapter 7

Propeller pump versus Intra Aortic Balloon Pump

Published as:

Dekker ALAJ, Reesink KD, van der Veen FH, van Ommen GVA, Geskes GG, Soemers ACM, Maessen JG. Efficacy of a new Intra Aortic Propeller Pump versus the Intra Aortic Balloon Pump: an animal study. Chest 2003;123:2089-2095.

7.1 Abstract

Objective
Compare the efficacy of a new Intra Aortic Propeller Pump to provide hemodynamic support to the Intra Aortic Balloon Pump (IABP) in an acute mitral regurgitation (MR) animal model.

Background
A new intra aortic propeller pump (Jomed Reitan Catheter Pump) has recently been introduced. The pump's aim is a reduction in afterload via a deployable propeller placed in the high descending aorta which can be set at rotational speeds up to 14000 rpm.

Methods
In nine calves, acute MR was created by placing a vena cava filter in the mitral valve. The propeller pump was tested at 6000, 10000 and 14000 rpm and compared to 1:1 IABP support. Cardiac output, coronary blood flow, carotid artery flow, ascending and abdominal aortic pressure, left atrial pressure and LV pressure-volume loops were recorded.

Results
The propeller pump caused a rpm-dependent reduction of mean ascending aortic pressure reaching -10mmHg ($p<0.05$) at 14000 rpm. However, cardiac output did not improve (2.6±0.7 to 2.5±1.1 l/min, p=NS) and diastolic coronary flow and carotid flow (47±16 to 35±15 cl/min, $p<0.05$) were reduced. The IABP improved cardiac output, carotid and diastolic coronary flow.

Conclusions
In this acute MR animal model, the propeller pump reduced afterload but left out positive effects on cardiac output, which resulted in reduced perfusion of the upper body and the coronary circulation. Therefore, the IABP gives better hemodynamic support than the new propeller pump in calves with acute mitral regurgitation.

7.2 Introduction

Circulatory support by the Intra Aortic Balloon Pump (IABP) is indicated in acute heart failure or cardiogenic shock either unresponsive to medical therapy or accompanied by acute mitral regurgitation[1,2]. The mechanism of the IABP is afterload reduction and an increase in coronary perfusion[1]. However, in some patients IABP support is not sufficient to maintain adequate circulation and other circulatory support devices may be indicated[1,3].

Recently, a new device to continuously reduce afterload has been developed: the Intra Aortic Propeller Pump (Jomed Reitan catheter pump, Jomed, Helsingborg, Sweden)[4]. It is a propeller-based pump placed in the high descending aorta with propeller rotational speeds up to 14000 rpm. Like the IABP, the aim of the pump is to reduce pressure proximal to the pump thereby reducing the afterload of the left ventricle. A secondary proposed benefit is the augmentation of perfusion distal to the pump. In the first human application of the propeller pump, excellent results were reported[5].

In the present study the efficacy of the new propeller pump to support circulation is compared to the intra aortic balloon pump in an animal model of cardiogenic shock due to acute mitral regurgitation.

7.3 Methods and Materials

7.3.1 Animal preparation

All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" (NIH publication 86-23, revised 1985) and the study was approved by our institution's animal ethics committee. Nine "Roodbont" calves with average weight 109 kg (76-148 kg) were premedicated with atropine (0.05 mg/kg s.c.). Anesthesia was induced with sodium thiopental (i.v.-bolus 15mg/kg) and maintained with a 1:2 mixture of O_2:N_2O and 2% halothane. After administration of muscle relaxant suxamethonium (i.v.-bolus 0.1 mg/kg) and analgetic buprenorfine (i.v.-bolus 0.01 mg/kg), a left thoracotomy was performed and ventilation was modified to give a peak end-expiration pressure of 5cm H_2O. Heparin (i.v.-bolus 100 IU/kg) was administered and the activated clotting time was measured and kept above 400 seconds during the experiment. Monitoring included ECG, blood pressure, oxygen saturation and capnography. The animals were sacrificed with an overdose of pentobarbital (i.v.-bolus 200 mg/kg).

7.3.2 Instrumentation

Under fluoroscopy, a Swan-Ganz thermodilution catheter (Arrow International, Reading, PA, USA) was advanced via the jugular vein. A conductance catheter, incorporating a pressure sensor (Sentron, Rhoden, the Netherlands), was placed via the right carotid artery in the left ventricle. The conductance catheter was connected to a conductance console (CD Leycom, Zoetermeer, the Netherlands) which was used in dual frequency mode[6]. Solid-state pressure catheters (Sentron, Rhoden, the Netherlands) were placed in the abdominal aorta via the left femoral artery, in the ascending aorta via the left carotid artery and in the left atrium through a small incision. Flow probes (Transonic Systems, Ithaca, NY) were placed on the ascending aorta, the left carotid artery and the left circumflex artery. The propeller pump was placed through a 14 French sheath in the femoral artery. After the measurements with propeller pump support, a 1:1 ECG triggered, 40ml Intra Aortic Balloon Pump (Datascope, Fairfield, NJ, USA) was placed via the same sheath.

The measurement protocol was creation of acute MR, measurement during unsupported acute MR, activation of the propeller pump at a certain rotational speed or IABP support, measurements during supported acute MR, relief of acute MR, stabilization. The IABP measurements were always done after the propeller pump measurements.

7.3.3 Acute mitral regurgitation model

As an animal model of cardiogenic shock, acute mitral regurgitation (MR) with a retrievable cage in the mitral valve, was chosen. This model simulates severe cardiogenic shock but is also reversible which allows multiple propeller rotational speeds to be tested as well as intra aortic balloon pumping without major deterioration of the hemodynamic state of the animal during the experiment.
An incision was made in the left atrium through which a retrievable steel wire cage (Günther tulip vena cava filter, William Cook Europe, Bjaeverskov, Denmark), was placed in the mitral valve (Figure 7-1). The amount of mitral regurgitation was defined as the percentage of left ventricular stroke volume flowing towards the atrium. This percentage was calculated by subtracting forward stroke volume (measured by an aortic flow probe) from left ventricular stroke volume (by conductance catheter) and dividing this by left ventricular stroke volume.

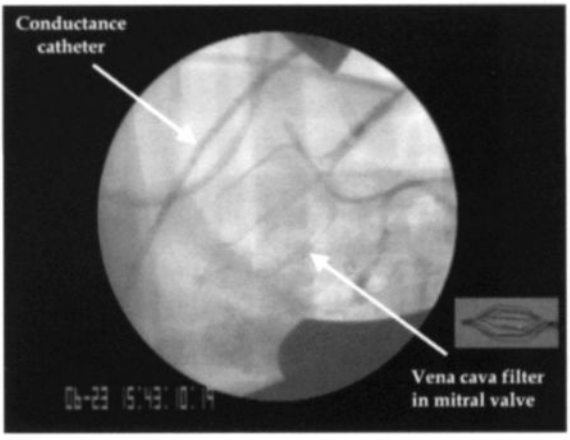

Figure 7-1: Fluoroscopic image of the vena cava filter opening the mitral valve to induce acute mitral regurgitation. The conductance catheter positioned through the aortic valve in the left ventricle, is also seen.

7.3.4 Intra Aortic Propeller Pump

The new intra aortic propeller pump is a support device with a deployable propeller (Figure 7-2) which is driven by a flexible central driveshaft[4]. The other end of the driveshaft is a permanent, disk shaped magnet which is placed in the driving unit. The driving unit consists of a rotating magnet that can be set at zero and up to 14000 rpm. The pump can only operate continuously, so no triggering is needed.
The propeller pump is placed in the descending aorta at a similar position as the intra aortic balloon. Once this position is reached, the propeller is

deployed (Figure 7-2) and is ready for use. A solution of 20% glucose and 5 IE/ml heparin was used at 25 ml/hr to purge and lubricate the pump.
The propeller is guarded by a basket which prevents contact between the propeller and the aortic wall. However, the aorta should have a diameter of at least 21mm to prevent stenting. For this reason, the aortic diameter was measured with fluoroscopy before insertion of the propeller pump. In all animals the diameter was between 21mm and 24 mm.

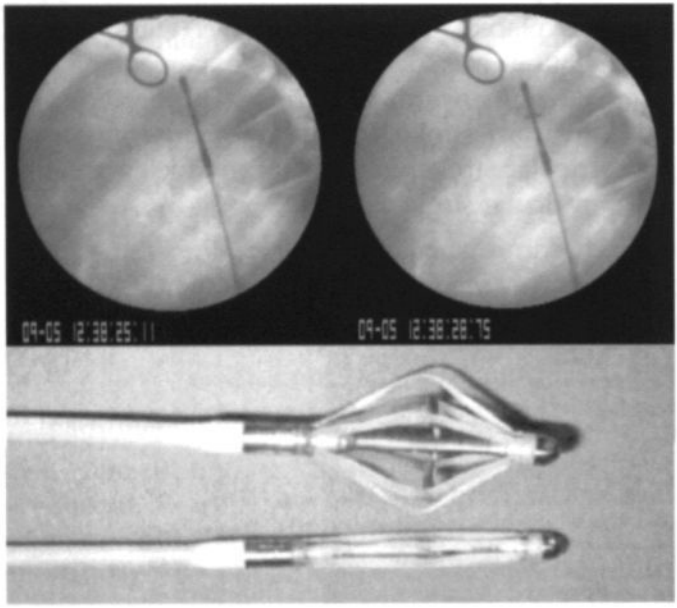

Figure 7-2: The intra aortic propeller pump with undeployed and deployed propeller.

7.3.5 Conductance calibration

Parallel conductance was determined by injecting 7.5 ml of 6.5% hypertonic saline in the pulmonary artery[7]. A 5 ml blood sample was collected and blood resistivity measured by a sampling cuvette (CD Leycom, Zoetermeer, the Netherlands)[8]. The slope factor was determined by comparing conductance derived stroke volume with the aortic flow prior to the creation of acute mitral regurgitation.

7.3.6 Statistical analysis

Statistically significant changes between unsupported acute MR and IABP or propeller pump supported acute MR were tested using a non-parametric, Wilcoxon signed ranks test. Significance was assumed if the P-value was less than 0.05.

7.4 Results

7.4.1 Instrumentation

Placement of the new propeller pump was possible through the femoral artery in all animals. Placement and deployment of the propeller could be clearly visualized under fluoroscopy (Figure 7-2). Upon propeller pump activation, a linear relation between gradient across the propeller (mean abdominal minus mean ascending aortic pressure) and rotational speed was found (Figure 7-3).

In all animals severe acute mitral regurgitation could be created with a mean regurgitant fraction of 65% (range 36-79%). This regurgitation resulted in cardiogenic shock with low cardiac output, a decreased aortic blood pressure, and a high left atrial pressure.

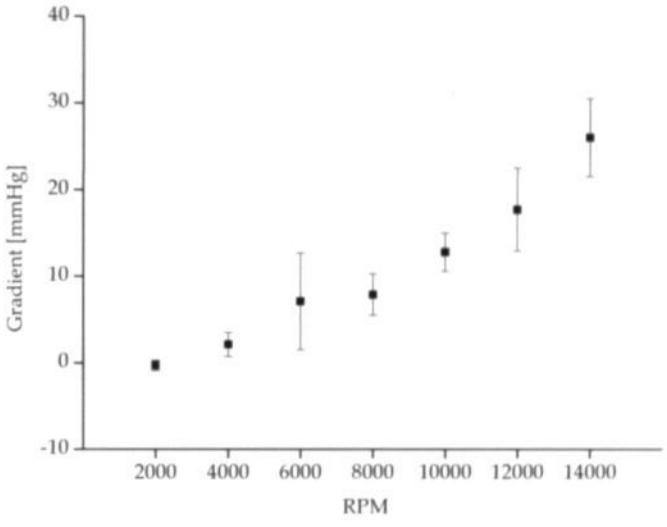

Figure 7-3: Pressure gradient across the propeller at different rotational speeds.

7.4.2 Comparison of baseline values

As the protocol dictated that the propeller pump measurements were done before the IABP measurements, the propeller pump and IABP baseline hemodynamic state may have been different. To exclude this, a non-parametric Friedman test was performed on cardiac output and on mean ascending aortic blood pressure recorded during unsupported acute mitral regurgitation just prior to the activation of 6000, 10000 and 14000 propeller pump or 1:1 IABP support. No significant difference in hemodynamic state could be found.

7.4.3 Hemodynamic effects of propeller pump and IABP

All hemodynamic data are given in Table 7-1. It shows that the propeller pump at 6000rpm had no significant effect on the circulation except for a small increase in abdominal aortic pressure. At 10000 and 14000rpm, clear effects were visible. Afterload, mean ascending aortic pressure and left ventricular peak systolic pressure, were decreased. Left atrial pressure simultaneously decreased, but this did not result in a smaller end-diastolic volume and therefore left ventricular preload was preserved. At 14000rpm, left ventricular contractility was depressed as seen by the decrease in stroke work and $dPdt_{max}$. Cardiac output was unaffected by propeller pump support, but mean carotid artery and diastolic coronary flow were decreased.

Mean coronary flow was maintained which, together with the decreased diastolic fraction, suggested a shift from diastolic to systolic coronary flow. At 14000rpm, coronary resistance was significantly reduced (Table 7-1).

A number of these observations are seen in the example given in Figure 7-4, where ascending aortic pressure, coronary flow and carotid artery flow are depicted when the propeller pump was switched off from 14000 to 1000 rpm. Ascending aortic pressure and especially diastolic carotid artery flow recovered when the pump was switched off. Coronary flow initially increased but stabilized after 20 seconds. The shift from systolic to diastolic flow is also evident in this example.

Switching on the IABP did not change left ventricular function as contractility (stroke work, $dPdt_{max}$), afterload (maximal left ventricular pressure) and preload (end-diastolic volume) and left ventricular stroke volume, were all unaffected by IABP activation. The IABP's main effect seems to be a reduction of mitral regurgitation which had a positive effect on the major hemodynamic parameters: cardiac output, mean aortic pressure and carotid flow. Furthermore, the counterpulsation increased diastolic coronary flow although mean coronary flow was unchanged.

Table 7-1: Hemodynamic changes before and during support with the propeller pump at various speeds and 1:1 IABP

		6000rpm		10000rpm		14000rpm		IABP 1:1	
		Off	On	Off	On	Off	On	Off	On
HR	[bpm]	131 ± 9	133 ± 9*	134 ± 13	137 ± 13	136 ± 13	138 ± 16	120 ± 25	122 ± 26
CO	[l/min]	2.5 ± 0.8	2.5 ± 1.1	2.5 ± 0.6	2.4 ± 0.7	2.6 ± 0.7	2.5 ± 1.1	2.2 ± 1.0	2.8 ± 1.2*
LVSV	[ml]	65 ± 28	66 ± 24	66 ± 30	68 ± 31	75 ± 43	71 ± 36	63 ± 37	65 ± 39
MR	[%]	62 ± 10	62 ± 11	70 ± 7	72 ± 9	70 ± 11	72 ± 11	66 ± 14	59 ± 17*
Qcar	[cl/min]	45 ± 12	44 ± 11	46 ± 16	43 ± 12	47 ± 16	35 ± 15*	37 ± 20	45 ± 23*
AOPasc	[mmHg]	51 ± 9	50 ± 10	54 ± 11	49 ± 12*	52 ± 9	42 ± 10*	45 ± 8	50 ± 9*
AOPabd	[mmHg]	51 ± 9	57 ± 11*	54 ± 11	62 ± 12*	52 ± 9	68 ± 12*	45 ± 8	54 ± 11*
Gradient	[mmHg]	-	7 ± 6*	-	13 ± 2*	-	26 ± 5*	-	4 ± 6
LVPmax	[mmHg]	62 ± 10	62 ± 11	65 ± 12	61 ± 13*	63 ± 11	57 ± 8*	55 ± 13	55 ± 12
LAP	[mmHg]	20 ± 7	20 ± 9	21 ± 11	19 ± 10*	20 ± 9	17 ± 9*	17 ± 8	17 ± 9
EDV	[ml]	101 ± 62	101 ± 62	101 ± 58	100 ± 60	111 ± 53	100 ± 49	108 ± 82	106 ± 83
dPdtMax	[mmHg/s]	729 ± 254	741 ± 257	772 ± 263	729 ± 313	737 ± 310	651 ± 222*	564 ± 206	590 ± 210
SW	[g m]	32 ± 19	33 ± 20	37 ± 23	36 ± 25	39 ± 28	34 ± 24*	28 ± 19	29 ± 20
$Qcor_{MEAN}$	[ml/min]	59 ± 34	61 ± 31	58 ± 29	58 ± 31	60 ± 28	57 ± 28	52 ± 26	55 ± 23
$Qcor_{PEAK\ DIA}$	[ml/min]	218 ± 55	210 ± 48	225 ± 46	181 ± 62*	224 ± 32	139 ± 36*	146 ± 71	391 ± 139*
DF	[%]	89 ± 24	83 ± 27	81 ± 16	67 ± 18*	75 ± 15	45 ± 27*	65 ± 20	94 ± 17*
AOPasc/Qcor	[mmHg min/cl]	9.8 ± 5.8	8.6 ± 4.2	9.9 ± 5.9	9.2 ± 5.4	9.4 ± 3.8	8.0 ± 4.1*	9.2 ± 2.7	9.6 ± 3.0

AOPabd: Mean abdominal aortic pressure; AOPasc: Mean ascending aortic pressure; AOPasc/Qcor: Index for coronary resistance, Mean ascending aortic pressure divided by mean coronary flow; CO: Cardiac output; DF: Diastolic fraction, mean diastolic coronary flow divided by mean coronary flow; dPdtMax: Maximal left ventricular pressure derivative; EDV: Left ventricular end-diastolic volume; Gradient: Difference between ascending and abdominal aortic pressure; HR: Heart rate; LAP: Mean left atrial pressure; LVPmax: Maximal left ventricular pressure; LVSV: Left ventricular stroke volume; MR: Mitral regurgitation; Qcar: Mean carotid artery flow; $Qcor_{MEAN}$: Mean coronary flow; $Qcor_{PEAK\ DIA}$: Peak diastolic coronary flow; SW: Left ventricular stroke work. All data shown are values averaged over 10 heart beats at end espiration breath-hold. *p<0.05 on versus off

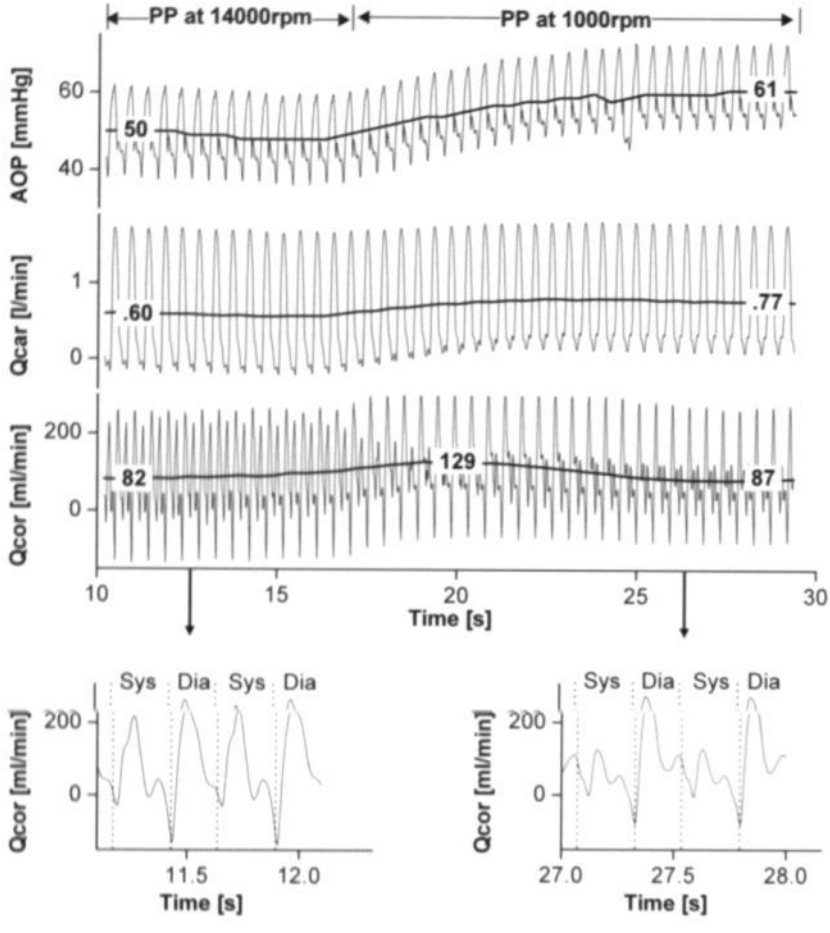

Figure 7-4: Top three panels: Example of changes in ascending aortic pressure, carotid flow and coronary flow when the propeller pump support is suddenly switched off from 14000 rpm to 1000 rpm. The thick line and the bold values indicate mean value.
Bottom panel: Coronary flow in detail during systole and diastole with the propeller pump at 14000 rpm (left) and 1000 rpm(right).

7.5 Discussion

7.5.1 Afterload reduction by the propeller pump

In this study we investigated a new intra aortic propeller pump for afterload reduction. It shows that the propeller pump is indeed able to reduce mean ascending aortic pressure by on average 10 mmHg and systolic left ventricular pressure by 6 mmHg at 14000 rpm (Table 7-1). Simultaneously, an increase in abdominal aortic pressure was observed. This gradient between ascending and abdominal aortic pressure is dependent on the rotational speed of the propeller pump (Figure 7-3) and reached 26mmHg at 14000rpm (Table 7-1). From in vitro studies, it is known that this gradient also depends on the aortic diameter, with the propeller pump being less effective in larger aortas[4]. As all animals in this study had comparable aortic sizes (21 to 24 mm) this phenomenon could not be examined.

7.5.2 Effect of the propeller pump on coronary flow

During propeller pump support at high rotational speeds, diastolic coronary flow is reduced (Table 7-1). This is a direct result of the lower ascending aortic pressure during diastole. However, net coronary flow is unaffected. This suggests an increased systolic contribution to the flow and thus a reduced diastolic fraction which is confirmed in Table 7-1. Two factors are likely to cause this increased systolic contribution to coronary flow. First, we observed a reduction in coronary resistance which may imply coronary vasodilatation during propeller pump support, as seen in the example of Figure 7-4. Second, left ventricular systolic pressure is reduced during propeller pump support which will lower systolic tissue pressure and decrease resistance to systolic flow[9].

During 1:1 IABP support diastolic coronary flow is increased (Table 7-1) while net coronary flow is not. The increase in diastolic flow is known to be caused by the counterpulsation. Due to the increase in mean coronary resistance, mean coronary flow does not change. This suggests vasoconstriction as has been reported before in epicardial arteries in non-ischemic hearts[10].

The main difference between the IABP and the propeller pump is the counterpulsating versus continuous nature of the pumps. The continuous nature of the propeller pump sucks blood towards the pump during diastole which explains the reduction in diastolic coronary and carotid artery flow (Table 7-1 & Figure 7-4). An obvious solution would then be to drive the propeller in a counterpulsating manner. However, the driveline

and the propeller itself are unable to withstand the forces generated by stopping let alone reversing the propeller every heart beat.

In conclusion, the propeller pump and the IABP have opposite effects on coronary flow. The propeller pump favors systolic coronary flow, while the IABP increases diastolic coronary flow. As diastolic flow is crucial to perfuse the subendocardial myocardium[11], it is likely that IABP support gives better subendocardial perfusion than propeller pump support.

7.5.3 Effect of the propeller pump on cardiac output

Although the propeller pump reduced afterload, this did not result in more cardiac output in this animal model. It is important to realize that in this acute mitral regurgitation model, the amount of mitral regurgitation and thus cardiac output is determined by the ratio of the impedance of the aorta versus the retrograde impedance during systole. Table 7-1 shows that the pressure (and thus the impedance) of the aorta is lower, but that left atrial pressure (or retrograde impedance) is lower as well during propeller pump support. The lower aortic pressure therefore does not result in less mitral regurgitation. In contrast, the IABP significantly reduced the amount of mitral regurgitation which has a positive effect on cardiac output.

While this explains why mitral regurgitation is not decreased upon propeller pump activation, it does not answer the more important question: Why is left ventricular stroke volume not increased with lower afterload? First, it should be noted that although the propeller pump creates a pressure gradient in the aorta of up to 26 mmHg at 14000rpm, the average reduction in mean ascending aortic pressure is 10 mmHg and the reduction in left ventricular systolic pressure is only 6mmHg (Table 7-1). The latter can be explained by the observation that the propeller pump reduces pressure continuously rather than only during systole and the fact that left ventricular afterload is determined by the aortic and the atrial pressure in this mitral regurgitation model.

Still, upon propeller pump activation, one would expect stroke work to remain similar with the lower afterload, which would result in more left ventricular stroke volume. This does not occur and consequently, stroke work is reduced which is statistically significant when the propeller pump is set at 14000 rpm. Now the concept of preload recruitable stroke work[12], states that a reduction in stroke work at similar preload (end diastolic volume does not change) implies less contractility. The decrease in $dPdt_{max}$ is also an indication of a loss of contractility.

We therefore conclude that left ventricular stroke volume is not increased with lower afterload because contractility of the left ventricle is reduced

with propeller activation at 14000rpm. This reduction in contractility may be linked to the observed reduction in diastolic coronary flow.

7.5.4 Redistribution of blood by the propeller pump

As mentioned above, the propeller pump did not increase cardiac output. Without an increase in cardiac output, the propeller pump will merely shift blood from the upper to the lower body. This was confirmed by the significant reduction in carotid artery flow and increase in abdominal aortic pressure at 10000 and 14000 rpm. This has an important clinical implication: In patients in cardiogenic shock where the propeller pump is applied, cardiac output should be closely monitored and if cardiac output does not increase, a reduction in flow to the brain should be expected.

7.5.5 Study Limitations

In this study the propeller pump and the IABP were tested in animals with acute mitral regurgitation, which is present in only 10% of cardiogenic shock patients[13]. In patients requiring hemodynamic support due to a different pathology, continuous afterload reduction offered by the propeller pump may be more beneficial. Further animal studies with ischemic heart disease, right ventricular failure or aortic regurgitation models may answer this question.

Finally, this study was designed as a proof-of-principle study and not as a safety study. However, a propeller rotating at such a high speed in the aorta raises important safety issues such as hemolysis and thrombogenesis. Future studies should address this problem.

7.5.6 Conclusion

In calves with acute mitral regurgitation, the intra aortic propeller pump has no significant hemodynamic effect at a setting of 6000rpm and a negative effect on general hemodynamics at 10000 and 14000 rpm. In contrast, the IABP at 1:1 assist has a profound positive effect on the systemic and coronary circulation. The IABP therefore provides better circulatory support than the new propeller pump in calves with acute mitral regurgitation.

7.6 References

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Chapter 8

Future pressure-volume loops in cardiac surgery

8.1 Introduction

In this thesis pressure-volume loops were applied to answer research questions in cardiac surgery. This has been typical for pressure-volume applications in general, not only in cardiac surgery: Pressure-volume loops have mainly been applied in (pre)clinical research such as evaluation of new diagnostic techniques, drugs or other treatments. In contrast, clinical decision making in individual patients is rarely done using pressure-volume loops, and therefore the role of pressure-volume loops in daily health care is very limited.

This chapter will discuss the question: Will there be clinical applications of pressure-volume loops in future cardiac surgical patients? To answer such a question, one has to identify the future cardiac surgical patient, and determine whether pressure-volume loops can give valuable information in these patients.

8.2 Cardiac surgery and heart failure

Currently, the vast majority of patients at a cardiac surgery department are treated for coronary artery disease or valvular disease. More recently, cardiac surgeons have begun to treat arrhythmia patients with procedures such as epicardial ablation for atrial fibrillation[1]. But despite the importance of these three patient groups, there are two reasons why the heart failure patient is the cardiac surgical patient of tomorrow.

First, the number of congestive heart failure patients is steadily increasing and is estimated at 2.2% of persons 45 year or older which corresponds to at least 150.000 patients in the Netherlands alone[2].

Second, medical treatment of heart failure seems to be at a dead-end as trials with new drugs all show minimal benefit to the patient. New hopes for heart failure treatment are therefore non-pharmacological: Resynchronization therapy, surgical ventricular remodeling, mechanical support and cell therapy. Cardiac surgeons will play a crucial role in these four treatments.

8.3 Pressure-volume loops in surgical heart failure treatment

Resynchronization therapy

In heart failure patients with left bundle branch block, one treatment option is left or bi-ventricular pacing. This application of pacing is also referred to as resynchronization therapy and has a well documented benefit[3]. In most patients the pacing leads are placed via catheterization of the coronary sinus. However, these leads can also be placed on the epicardium in a minimal invasive surgical procedure. The best position of the pacing lead and the proper time delay can be determined with pressure-volume loops.

Mechanical support

Mechanical support can be used to recover the failing heart. This has long been known in post-cardiotomy and myocarditis patients[4], but recent reports suggested that recovery of chronic heart failure is also possible: Young cardiomyopathy patients who received what was meant to be a permanent assist device, showed such a strong recovery of cardiac function that their assist device could safely be removed[5]. This raises challenging questions such as: Can recovery of heart failure be achieved with mechanical support in larger patient population? Which patients would benefit from such a treatment? How can we measure recovery? Can drugs speed up the process? As ventricular function and heart failure can be quantified and characterized with pressure-volume analysis, it is most likely the ideal method to answer these questions.

Procedures aimed at changing the geometry of the failing heart

Surgical treatment of dilated cardiomyopathy has already been mentioned as one of the areas where pressure-volume loops have a proven track record[6-8]. As heart failure emerges as one of the main cardiac diseases of the coming years, new devices and surgical procedures will continue to emerge that are targeted at surgically improving the geometry of the failing heart (Acorn[9], Myosplint[10], Surgical Ventricular Restoration[11]).
Pressure-volume loops offer the opportunity to validate these procedures and to determine if the better systolic function associated with these procedures is not counterbalanced by a worse diastolic function[12,13]. For the individual patient, pressure-volume loops might be used for correct patient selection and to direct post-operative care towards treating remaining or new systolic and diastolic dysfunction.

Cell transplantation

Perhaps the most intriguing concept to treat heart failure is to replace the diseased myocardium with cells that can perform cardiac work[14]. Goal of cell transplantation is to improve the contractility of the heart. Pressure-volume loops have the unique property to be able to measure contractility quantitatively. Eventually the decision will have to be made if the concept works, how much cells to implant in the individual patient, to evaluate the patients over time and to decide to begin or repeat treatment. To answer questions like these, pressure-volume loops may be beneficial.

8.4 Conclusion

Pressure-volume loops in cardiac surgery are here to stay. Researchers will always appreciate the fact that from a thermodynamical, physiological and empirical viewpoint, pressure-volume loops are central to our understanding of the heart. With the upcoming interest in ventricular function by clinicians dealing with heart failure patients, it can be expected that the interest in pressure-volume loops will steadily rise.

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Summary

The heart consists of two pumps: the right and left ventricle. The function of the heart is to displace blood from a low-pressure reservoir (the atria) to a high pressure reservoir (the pulmonary artery and the aorta). The change in pressure and volume inside the left ventricle during a heart beat can be described in four phases:

1) In the contraction phase the heart muscle contracts thereby raising pressure inside the ventricle. No blood enters or leaves the ventricle in this contraction phase, the phase is isovolumic. 2) When the pressure inside the ventricle becomes higher than the pressure in the aorta the ejection phase starts. In this phase the volume of the ventricle reduces while pressure remains more or less constant. 3) At the end of ejection, the relaxation phase occurs in which the heart muscle relaxes and pressure drops inside the ventricle. The relaxation phase is also isovolumic. 4) Once ventricular pressure is lower than atrial pressure, the filling phase commences. During this phase the ventricle is filled from the atrium and ventricular volume increases at slightly increasing pressure. After filling is complete, another heart cycle starts.
If pressure and volume during a heart cycle are plotted in the xy-plane, one gets a square loop: the pressure-volume loop.

Pressure-volume loops offer insight in the function of the heart, just like they do in other systems such as steam engines or water pumps. **Chapter 1**, the introduction, discusses in detail what information can be obtained from pressure-volume loops. Furthermore the various techniques to measure pressure-volume loops are compared with emphasis on the conductance catheter technique. Finally past applications of pressure-volume loops in cardiac surgery are reviewed and it is found that few studies are conducted in this field.

This thesis deals with new applications of the conductance catheter technique in three typical cardiac surgery subjects: valvular disease, coronary artery bypass grafting and mechanical support.

Valvular disease

Aortic valve stenosis is a common disease in which the aortic valve becomes too narrow thereby making ejection more difficult. To be able to eject through the stenotic valve, the left ventricle thickens and increases its muscle mass (hypertrophy). With progressive narrowing, the hypertrophy may be insufficient to maintain cardiac output and heart failure may develop. Therefore, a patient with symptomatic aortic valve stenosis should

receive surgery in which the aortic valve is replaced by a prosthetic valve. In most patients, the hypertrophy and symptoms disappear after the operation; the disease is reversible. But in an important group of patients, hypertrophy and symptoms do not improve or even worsen. These patients may have been operated too late, at a stage where the disease has become irreversible. In **chapter 2**, pressure-volume loops are used to describe in detail the left ventricular function just before the aortic valve is replaced. After follow-up some of the measured parameters may prove to predict post-operative outcome and especially the reversibility of the disease.

In aortic valve regurgitation, blood leaks from the aorta to the left ventricle during the relaxation and filling phase. The relaxation phase is therefore no longer isovolumic. Conceptually a non-isovolumic relaxation phase can be detected in a pressure-volume loop, but this has never been tried. In **chapter 3**, the diagnosis aortic valve regurgitation with pressure-volume loops is compared to echocardiography. It turns out that aortic valve regurgitation is sometimes visible in a pressure-volume loop but that the correlation with echocardiography is disappointing.

Off-Pump Coronary Artery Bypass Grafting

The coronary arteries supply the heart with blood. The most common heart disease is the disease in which one or more of the coronary arteries become too narrow leading to a reduced supply of blood and thus oxygen downstream: the downstream region becomes ischemic. An ischemic part of the heart muscle will not be able to function properly and the muscle cells will eventually die. Coronary artery bypass grafting (CABG) is commonly performed in these patients. In this cardiac surgical procedure a new vessel is placed between the aorta and the ischemic muscle.

In conventional CABG the heart is arrested with the use of cardiopulmonary bypass, in order to be able to suture the vessel to the heart (anastomosis). However, the cardiopulmonary bypass has known complications (e.g. neurological) and thus alternative procedures are intensively studied. One possibility is to perform beating heart CABG or off-pump CABG (OPCAB) in which only the anastamosis site is stabilized with a tissue stabilizer. The stabilizer can also be used to turn and lift the heart in order to facilitate an anastomosis on the inferior and posterior wall. However, this so-called cardiac tilting causes hemodynamic complications such as a lower blood pressure and cardiac output, which limits the use of this technique. In **chapter 4** pressure-volume loops are used to show the filling of the right ventricle is the cause of the hemodynamic complications. In **chapter 5** a new right ventricular support device is tested which is meant to support the right ventricle during the tilting procedure. However, it is

concluded that this new pump can only partially restore normal hemodynamics.

Mechanical support

Mechanical support of the heart is indicated when the heart itself does not have enough output to maintain a viable circulation despite maximal medical treatment. This pump failure can occur due to an endocarditis, a large myocardial infarct, after open-heart surgery, acute valvular regurgitation or due to acute worsening of chronic heart failure. Nowadays the intra-aortic balloon pump (IABP) is the most common mechanical support. However, the supporting characteristic of the IABP are not well established in cardiogenic shock due to acute mitral valve regurgitation. **Chapter 6** describes a study with pressure-volume loops which shows that the IABP reduces mitral regurgitation and has thus a very positive effect on cardiac output and the circulation as a whole.

The IABP is minimal invasive but often has only a limited effect on the circulation. Other mechanical support modalities (extracorporeal life support, assist device) are more effective than the balloon pump in supporting the circulation, but are also much more invasive with more serious complications. A minimal invasive device with better supporting characteristics than the IABP would be very useful in cardiology and cardiac surgery. In **chapter 7** a new minimal invasive propeller pump, which possibly meets these criteria, is compared to the intra-aortic balloon pump. This pump is minimal invasive but the study shows that it is less effective than the IABP to support the circulation.

In the final **chapter 8**, possible future applications of pressure-volume loops in cardiac surgical patients are presented. It is concluded that especially the growing number of heart failure patients may benefit from pressure-volume analysis.

Samenvatting

Het hart bestaat uit twee pompen: de rechter en linker hartkamer. Het is de taak van de kamers om een bepaald volume bloed te verplaatsen van een laag druk compartiment (rechter en linker boezem) naar een hoog druk compartiment (long- en lichaamslagader/aorta). De verandering in druk en volume in de linker hartkamer gedurende een hartcyclus kan in vier fases worden beschreven:

1) In de contractie fase trekt de hartspier samen waardoor de druk in de hartkamer verhoogt. Aangezien tijdens deze fase geen bloed het hart in- of uitstroomt geschiedt deze drukverhoging op constant kamer volume; de contractiefase is isovolumisch. 2) Als de druk in de linker hartkamer hoger is dan de druk in de aorta, dan opent de aortaklep en begint de ejectiefase. In deze fase vermindert het volume in de hartkamer maar blijft de druk min of meer constant. 3) Aan het einde van de ejectie, ontspant het hart, valt de druk in de kamer en sluit de aortaklep. Deze relaxatiefase is ook weer isovolumisch. 4) Als de druk in de hartkamer lager is dan de druk in de boezem, dan opent de mitralis klep en begint de vullingsfase. Tijdens de vullingsfase stijgt het volume van de kamer onder licht oplopende druk. Als de vulling van het hart is voltooid, begint een nieuwe hartcyclus.

Als de druk en het volume tegen elkaar worden uitgezet gedurende een hartslag, dan levert dat een vierkante lus op welke iedere hartslag tegen de klok in wordt doorlopen. Dit wordt ook wel een druk-volume lus genoemd (pressure-volume loop).

Druk-volume lussen leveren inzicht in het functioneren van het hart, zoals ze ook gebruikt kunnen worden voor het beschrijven van andere pompen zoals stoommachines en waterpompen. In **hoofdstuk 1**, de introductie, wordt in detail besproken welke informatie uit de druk-volume lussen van het hart kan worden verkregen. Verder wordt aandacht besteed aan de meetmethode, waarbij de nadruk ligt op de meting van druk-volume lussen met een zogenaamde conductantie catheter. Vervolgens worden de hartchirurgische toepassingen van druk-volume lussen besproken en blijkt dat deze techniek nog maar mondjesmaat wordt toegepast binnen de hartchirurgie.

Dit proefschrift behandelt de toepassing van druk-volume lussen van het hart in drie hartchirurgische onderwerpen: klepziekten, bypass operaties en mechanische ondersteuning.

Klepziekten

De klep tussen de linker hartkamer en de aorta, de aortaklep, kan lekken (aorta klep insufficiëntie) of vernauwd zijn (aortaklepstenose). In het geval van aortaklepstenose verdikt de hartspier (hypertrofie) om zo voldoende druk te ontwikkelen om door de vernauwde klep te kunnen ejecteren. Op een gegeven moment in de ziekte, kan de hypertrofie de stenose niet meer compenseren hetgeen uiteindelijk resulteert in hartfalen. Een patiënt met belangrijke aortaklepstenose en symptomen dient derhalve te worden geopereerd waarbij de aortaklep vervangen wordt door een prothese. In de meeste patiënten vermindert de hypertrofie na de operatie en verdwijnen de klachten; de ziekte is dus omkeerbaar. Echter, in een belangrijke groep patiënten blijven de klachten en hypertrofie bestaan of worden ze zelfs erger. Deze patiënten zijn waarschijnlijk te laat geopereerd waardoor de verslechtering van de hartspier onomkeerbaar is geworden. In **hoofdstuk 2** worden druk-volume lussen gebruikt om vlak voor de klepvervanging de functie van de linker kamer tot in detail te beschrijven. Door deze patiënten te vervolgen blijken wellicht sommige van de gemeten parameters voorspellend te zijn voor het uitblijven van de vermindering in klachten en hypertrofie.

Als de aortaklep lek is, stroomt er bloed uit de aorta naar de hartkamer tijdens de relaxatie- en vullingsfase, de relaxatiefase is dus niet langer isovolumisch. Dit moet te detecteren zijn in druk-volume lussen, maar dit is nog nooit geprobeerd. In **hoofdstuk 3** wordt de diagnose aortakleplek met behulp van druk-volume lussen vergeleken met echocardiografie. Het blijk dat aortkleplek soms te zien is in druk-volume lussen, maar dat de correlatie met echocardiografie matig is.

Bypass operatie op een kloppend hart

De kransslagaders ontspruiten in de aorta en voorzien het hart zelf van bloed. De meest voorkomende hartziekte is vernauwing van de kransslagaders. Door deze vernauwing krijgt het hartweefsel benedenstrooms van de vernauwing te weinig bloed en zuurstof (ischemie). Ischemisch hartspierweefsel kan niet meer functioneren en zal uiteindelijk afsterven. Om dit te voorkomen, wordt in een bypass operatie een extra vat aangelegd van de aorta naar het ischemische hartspierweefsel.

Om het vat te kunnen vasthechten op de hartspier (anastomose) wordt tijdens een conventionele bypass operatie het hart stilgelegd met behulp van een hart-long machine. De hart-long machine heeft ook complicaties (m.n. neurologische) en derhalve wordt gezocht naar alternatieven. Een mogelijkheid is de operatie uit te voeren op het kloppende hart waarbij, met behulp van een stabilisator, alleen de plek van de anastomose wordt

stilgelegd. Om anastomoses op de achter- en onderwand te kunnen maken, moet het kloppende hart worden opgetild en gedraaid hetgeen ook kan met de stabilisator. Deze procedure gaat echter gepaard met hemodynamische complicaties zoals een val in bloeddruk en slagvolume. Deze complicaties beperken de mogelijkheden van de kloppend hart bypass operatie.

In **hoofdstuk 4** wordt met behulp van druk-volume lussen aangetoond dat de slechtere vulling van de rechter kamer de oorzaak is van de hemodynamische complicaties. In **hoofdstuk 5** wordt onderzocht of een nieuwe rechter ventrikel ondersteuningspomp tijdens het optillen van het hart nuttig is. Geconcludeerd wordt dat deze nieuwe pomp maar gedeeltelijk de hemodynamische complicaties kan voorkomen.

Mechanische ondersteuning

Ondersteuning van het hart met een mechanische pomp is nodig als het hart zelf niet meer genoeg pompt ondanks maximale medicinale behandeling. Dit pompfalen kan optreden bij ontsteking van de hartspier, na een groot hartinfarct, acuut hartklep lek, na een hartoperatie, of bij acuut verergeren van chronisch hartfalen. Op dit moment wordt de intra aorta ballon pomp het meest toegepast als mechanische ondersteuning. Echter, in het geval van acuut mitralis klep lek (klep tussen de linker boezem en kamer) is deze pomp nog niet goed gekarakteriseerd. In **hoofdstuk 6** wordt een onderzoek beschreven waarin, met behulp van druk-volume lussen, wordt gedemonstreerd dat de ballon pomp het mitralis klep lek vermindert, hetgeen een zeer gunstig effect heeft op de circulatie.

De ballon pomp maakt minimaal inbreuk op het lichaam (minimaal invasief) maar heeft vaak slechts een beperkt positief effect. Andere vormen van mechanische ondersteuning (extra corporal life support, assist devices) zijn veel invasiever en kennen derhalve een hogere complicatiegraad, maar zijn wel veel effectiever dan een ballon pomp. Een systeem dat minimaal invasief en maximaal effectief is, zou zeer gewenst zijn in de hartchirurgie en cardiologie. **Hoofdstuk 7** beschrijft een nieuwe minimaal invasieve propeller pomp. Helaas blijkt uit deze studie dat de nieuwe pomp minder effectief is dan de ballon pomp.

Tenslotte wordt in **hoofdstuk 8** de mogelijke toekomstige toepassingen van druk-volume lussen besproken. Geconcludeerd wordt dat de techniek vooral nuttig zou kunnen zijn voor het groeiende aantal patiënten met hartfalen.

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André Dekker
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Biografie

André Dekker werd geboren op 20 juni 1974 te Eindhoven. Na het VWO op het Gymnasium Celeanum te Zwolle en het Sint Ludgercollege te Doetinchem, is hij in 1991 begonnen met de studie Technische Natuurkunde aan de Universiteit Twente. Deze studie heeft hij verbreed met een biomedische en bedrijfskundige aantekening. In 1996 heeft hij gereisd door Australië en stage gelopen op de afdeling radiotherapie van het Royal Adelaide Hospital. Hij is afgestudeerd in 1998 bij de vakgroep Technische Optica van de Universiteit Twente met als onderwerp de foto-akoestische detectie van bloedvaten in weefsel. In datzelfde jaar startte hij zijn specialisatie tot klinisch fysicus aan de Technische Universiteit Eindhoven en het Academisch Ziekenhuis Maastricht. Als onderdeel van deze opleiding heeft hij in 1999 stage gelopen bij Datex-Ohmeda in Louisville, Colorado, USA op het onderwerp weefseloptica. De eerste helft van deze opleiding werd in maart 2000 succesvol afgerond middels het behalen van de titel Master of Technology Design. In april 2001 ontving hij de Jonge Onderzoekers Prijs van de Nederlandse Vereniging voor Klinische Fysica voor zijn onderzoek naar mechanische ondersteuning tijdens kloppend-hart bypass operaties. In februari 2002 voltooide hij de opleiding en werd hij geregistreerd als algemeen klinisch fysicus. Sinds 1 maart 2002 werkt hij als klinisch fysicus bij de afdeling Cardio-thoracale Chirurgie van het Academisch Ziekenhuis Maastricht. Hij is getrouwd met Caroline Claessens en heeft twee kinderen, Noah en Zoé.